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UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	**January 4, 2007**
LISZIEWICZ, et al.	:	**Atty Docket No. RGT 9771**
Serial No. 10/081,922	:	**Group 1632**
Filed: 15 September 1998	:	**Examiner: Wilson**

For: Method of Delivering Genes into Antigen Presenting Cells of the Skin

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL[1]

In response to the Office Action bearing a mail date of May 4, 2006, the due date for which was extended one three months by petition and fee to November 4, 2006 (automatically extended to November 6), and a Notice of Appeal having been filed November 6, whereby the enclosed filing is due January 6, 2007 (automatically extended to January 8), kindly enter the enclosed Brief of record. A credit card form for the fee set forth in § 41.20(b)2 is enclosed. The Commissioner is authorised to charge any additional fees due, or credit any overage, to Deposit Account No. 50-0855. This page is enclosed in duplicate.

The applicant remains entitled to the previously-claimed small entity status.

Respectfully Submitted,

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[1] This paper is being forwarded by Express Mail Label ER 178973850 US to Mail Stop – Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on January 5, 2007. Signed Valerie E. Looper /Valerie E. Looper/

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The stamp below indicates the date of receipt of:

1. Appeal Brief, including (i) Real Party in Interest (ii) Related appeals and interferences, (iii) Status of Claims, (iv) Status of Amendments, (v) Summary of claimed subject matter, (vi) Grounds of rejection (viii) Argument, (viii) Claims Appendix (ix) Evidence Appendix and (x) Relatied Proceedings Appendi.x.

2. Certificate of Mailing by Express Mail Label NO. ER 178973850 US dated 5 January '07

4. Credit card payment form

all in USSN 10/081,922 re "Method of Delivering Genes into Antigen Presenting Cells of the Skin, by Lisziewicz and Lori 02/21/02, atty docket No. RGT 9771

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REAL PARTY IN INTEREST

The real party in interest in this case is Genetic Immunity, Inc., a Delaware corporation having an office at 8300 Greensboro Drive, McLean Virginia 22102.

RELATED APPEALS AND INTERFERENCES

As of January 4, 2007, there are no appeals and interferences related to this case.

STATUS OF CLAIMS

This case is a Division of USPN 6,420,176. Claims 1-22, 27, 29,34, and 36 have been cancelled. Claims 23-26, 28, 30-33, 35, and 37-43 have been finally rejected and are being appealed.

No Claims have been allowed in this case.

STATUS OF AMENDMENTS

No amendment was filed subsequent to the outstanding final rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is a division of United States Patent No. 6,420,176, which was drawn to a novel DNA complex for gene delivery. The present set of Claims contains only one independent claim, drawn to a method of transfecting antigen presenting cells.

Independent Claim 23 – Citations are to the application, found at item 15 (last item) of the Evidence Appendix.

Claim 23 relates to a method of transfecting (Defined page 6, lines 1-2) antigen presenting cells (defined page 2, lines 29-31) (Title, Abstract. Field of the Invention, page 2, lines 11-24), the steps comprising selecting a gene delivery complex (page 12, lines 32-33 and 35-37) that targets (page 11, line 9) antigen presenting cells (page 12, lines 23-30), comprising DNA (page 8, lines 26-30) and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives (page 14, lines 20-22), and applying the complex to the skin or mucosa surfaces of an animal (page 16, line 34), wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter (Supra, at page 8).

Description of the Drawings

In Fig. 2, the process for sugar-mediated gene delivery into cells expressing mannose-receptors is illustrated conceptually. Target cells (10), in this case, immature Langerhans cells having one or more mannose-receptors (12) are exposed to a gene-delivery complex (13) comprising a polyethylenimine-sugar (mannose) complexed with the foreign genetic material. The gene delivery complex (13) binds to the receptors (12) of the cell (10) and the PEI-man-DNA is incorporated into the cell via endocytosis in an endosome (14). The vector (PEI-man) has the property of breaking (15) the endosome , allowing the foreign genetic material to be released into the cell. The cell matures (16) and expresses proteins (17) coded by the foreign genetic material.

Fig. 7 reports experimental evidence that transcutaneous transduction of Langerhans cells results in migration of the cells and expression of the transferred gene. The figure is a series of color photographs which records green cells having DC morphology and expressing the green fluorescent protein, which is the product of the gene which was transferred via skin delivery. Panel A is a sample of a lymph node from a control mouse at 200x magnification. It exhibits a normal amount of background fluorescence. The same is true of Panel C, except that the magnification is 400x. Panel B is a sample from a lymph node of a mouse that was immunized by the transcutaneous application of a PEI-mannose-DNA complex. Panel D is the same as Panel B, except that the magnification is 400x. The fluorescence exhibits the bumpy morphology characteristic of dendritic cells expressing proteins.

Experimental Support in the Disclosure

This application discloses experiments that use of DNA in combination with PEI, PEI modified with various sugars, including mannose, galactose and glucose (in saline solution, Experiment 6 at page 21 line 15, Table 1), and DNA alone, DNA in combination with PEI and DNA in combination with PEI modified with mannose, each combined with a sugar (formulated in glucose solution, Experiment 8, page 22, line 35 , Table 2).

The present application also discloses how to modify the teachings of the closest prior art, namely the Behr reference, so that the claimed antigen presenting cells can be targeted via the mannose receptor as opposed to the asialoglycoprotein receptor (at least at page 14, line 37 – page 15, line 15, and Example 6, especially p. 21, lines 8-9 (use of sugars) and Example 7, especially page 21 lines 28-29 (uncharged particles) and page 22 lines 21-26 (control of charge via relative amount of PEI v. DNA).

The transduced cells are disclosed to be capable of provoking a CTL response (page 11, line 21) and proven to do so *in vitro* (Example 3), and *in vivo* (Example 4).

Experimental Support via Declaration

This application is further supported by a Declaration of Dr. J. Lisziewicz of April 27, 2001, filed May 1, 2001 in the parent patent application, enclosed at Evidence Appendix 3. This Declaration identifies one of the inventors, a prominent researcher in the field of the invention, discusses the correspondence between the animal model and the course of HIV infection in humans (Background paras. 1-3) the similarity of response to drug therapy (para. 4), and the therapeutic benefit of virus-specific T cell mediated immune responses (para. 5). This Declaration further compares the best-available drug treatment (Efficacy, para 1), an enhanced, innovative drug treatment (Efficacy, para 2), the limits of the innovative drug treatment (para. 3) and the novel immune therapy involving the use of a complex of PEI-mannose and plasmid DNA encoding an integrase-defective SHIV in sugar-water solution (paras. 4 and 5). The animals' response to treatment is discussed in detail (Efficacy, paras. 6-10), and summarized as showing increased CTL response associated with control of virus replication and improved survival time (Efficacy, paras. 11 and 12). The inventor states that the result, control of virus replication after the interruption of drug treatment during chronic infection or AIDS, is new. (Id.)

Experimental Support via Peer-Reviewed Articles by the Inventors

Additional data submitted by the inventors shows that the statements found in the application and the Declaration are acceptable for publication in peer-reviewed journals. These are:

Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/Aids" J Invest Dermatol, 2004 detailing the use of the presently claimed invention to produce CTL responses; (Evidence Appendix – 4)

Lisziewicz, et al., "Control of Viral Rebound through therapeutic immunization with DermaVir", AIDS 2005, 19:35-43 discloses studies showing low toxicity, enhanced viral control, and enhanced longevity; (Evidence Appendix – 5)

Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Type 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells J Virol. Aug 2001, p. 7621-7628, where the Examiner's technical questions about the differences between a replication-defective retroviral particle and plasmid DNA encoding the same are addressed. Expression of viral antigen by plasmid DNA is compared to that of the replication-defective control in primay human lymphocytes, macrophages, and dendritic cells in Fig. 1 b-d. (Evidence Appendix – 6)

Lori, et al., Cellular Immunity and DNA Vaccines for the Treatment of HIV/AIDS, Curr. Me. Chem. – Anti-infective agents, 2004, 3, 31-41, cited by the Examiner in support of an enablement rejection as allegedly indicating that the present invention has no value.

However, this reference shows "our DC targeted HIV vaccine, DermaVir, a topical, therapeutic vaccine that has demonstrated immunological and clinical benefits in rhesus macaques" at page 32, Column 1, 1st full para, lines 1-5 up. The article presents pre-clinical studies, page 38-39, a theoretical basis to explain why the vaccine differs from other vaccines (page 39, 2nd full para) and a suggestion for its treatment as a new antiretroviral approach complementary to that of various drug classes (page 39, paragraph bridging Cols. 1 and 2). (Evidence Appendix – 7)

Dependent Claims

Each dependent claim is argued separately, and each is supported in the text as follows:

24. The method of Claim 23, wherein the compound is selected from the group consisting of glucose and polyethylenimine derivatives. Example 10, page 24, lines 29-31 – glucose; Page 16, lines 27-28 – PEI derivatives

25. The method of Claim 24, wherein the polyethyleneimine derivative targets the mannose receptor found on the surface of antigen presenting cells. Page 7, lines 19-21.

26. The method of Claim 25, wherein the derivative is mannosylated polyetheylenimine. Example 8, page 22, lines 29-33

28. The method of Claim 23, wherein the complex is electrostatically neutral. The term "electrostatically neutral" is found at page 22, line 5, and an extended discussion as to how to use this trait is found at Example 7, page 21, line 30 – page 22, line 16. The neutral complex of PEI-mannose-DNA is disclosed to be more efficient than the neutralized complex of PEI-DNA at page 22, lines 19-21.

30. The method of Claim 28, wherein the complex comprises a 5:1 ratio of polyethylenimine derivative nitrogen per DNA phosphate. Example 7, page 22, lines 21-22.

31. The method of Claim 23, wherein the gene delivery complex is formulated in a glucose solution. Example 8, page 22, lines 35-36.

32. The method of Claim 31, wherein the glucose solution is 5-10% glucose. Example 8, page 22, lines 35-36.

33. The method of Claim 32, wherein the glucose solution is 8% glucose. Example 8, page 22, lines 35-36.

35. The method of Claim 23, further comprising one or more steps selected from the group consisting of receptor stimulation, toxin activation, tissue injury and cell injury. page 16, lines 37-38.

37. The method of Claim 23, wherein the protein is from a human immunodeficiency virus. Example 5, page 20, lines 22-26.

38. The method of Claim 37, wherein the human immunodeficiency virus is replication-defective. Example 1, page 18, lines 30-32.

39. The method of Claim 38, wherein the human immunodeficiency virus is integration-defective. Example 1, page 18, lines 30-32.

40. The method of Claim 23, wherein the DNA is a plasmid. Example 1, page 18, lines 30-32.

41. The method of Claim 23, wherein the cells are Langerhans cells. Page 2, line 20; Page 8, lines 1-3.

42. The method of Claim 29, wherein the complex comprises a 3:1 ratio of polyethylenimine nitrogen per DNA phosphate. Example 7, page 22, line 12.

43. The method of Claim 25, wherein the derivative is a sugar-modified polyethylenimine. Example 6, page 21, line 8.

REMARKS

Claims 23-26, 28, 30-33, 35, and 37-43 are currently under consideration. The Applicants have pointed out that these claims are founded on several distinguishable improvements included in the text of this application: effective transfection of antigen presenting cells *in vitro* using a material newly introduced in the gene therapy field by others (PEI), so that a CTL response could be obtained in vitro, a chemical modification of PEI to adapt it better to the Applicants' field of interest, immune therapy, development of alternatives to the chemical modification, including an elegantly simple, inexpensive modification, and a method of needless vaccination. The application contains experimental evidence that the Examiner admits demonstrates the method as claimed. Evidence of record includes a Declaration showing that therapeutic results, including enhanced longevity of animals with AIDS, has been of record in this case since the date of filing, February 21, 2002. Further, peer-reviewed articles by both the inventors and others showing that the text of the application is credible, and that therapeutic results have been obtained. A vaccine according to the currently claimed invention is in human clinical trials in two countries.

Priority

The Examiner has previously acknowledged that this case is a division of the parent patent, and stated that the claims are patentably distinct from the parent patent. The Examiner's position, that language in the Claims can convert an application from a division to a CIP where the text the application is unchanged, is unsupported by citation by the Examiner.

Response

This matter is discussed in detail under the heading "1. New Matter." Upon detailed review of the MPEP, the applicants have concluded that the position stated by the Examiner does not conform to ordinary USPTO practice or the applicable overarching law.

Specification

The Examiner states that the first line of the specification will have to be updated to indicate that the instant application is a CIP of 09/153198. The Examiner alleges that the preliminary amendment filed 2-21-02 claimed "mixtures thereof" of sugars, PEI and PEI derivatives, which is said not to have been contemplated in 09/153198. This issue is discussed below under the heading "1. New Matter."

The Examiner states the status of the application on pg 9, line 7, will have to be updated as necessary.

The status of the application on pg 13, line 36, will need updated as necessary.

The status of the application on pg 18, line 32, *will* need updated as necessary.

Response

The specification has been amended as required by the Examiner, and the status updates will be provided upon a change in status. Whether the application is properly characterized as a CIP is discussed below under the heading "1. New Matter."

Claim Rejections – 35 USC § 112

1. New Matter

The limitation of "one or more compounds selected from the group consisting of sugars, polyethyleni mine, and polyethylenimine derivatives" in claim 23 has support in the phrase "sugars, polyethylenimine, and polyethylenimine derivatives, and mixtures thereof' in the preliminary amendment on 2-21-02 in claim 23.

Response – New Matter

The applicants have previously pointed out the present question involves an objection to language in a claim, not an amendment to the abstract, specification, or drawings in the application. This rejection is not in keeping with the practice of the United States Patent and Trademark Office. The claim language is not properly rejectable as new matter (MPEP 2163.01; MPEP 2163.06, In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

The applicants have already pointed out that this limitation is supported by the text of the present application. See, for example the following from the Remarks section of the last Amendment: "The amendments to Claim 23 are supported at least at page 15, lines 6-8 and 16-17. The amendments are also supported at least at example 10 and Table 2, where DNA, PEI, and modified PEI were all formulated in 8% glucose, and that for the transcutaneous method, DNA formulated with sugar only was the most efficient gene delivery system."

This same information can be found in the parent patent, USPN 6,420,176 (Evidence – 1). It is undisputed that this patent discloses the use of DNA in combination with PEI, PEI modified with various sugars, including mannose, galactose and glucose (in saline solution, Experiment 6, Col. 14, line 63, Table 1), and DNA alone, DNA in combination with PEI and PEI modified with mannose (formulated in glucose solution, Experiment 8, Col. 15, final line, Table 2) and the surprising results for cutaneous delivery for DNA complexed with glucose alone is discussed (Example 10) *in the experiments*

found in the text of the parent patent. Applicants submit that the claim language cannot reasonably be construed as new matter.

2. Written Description.

Claims 37-39 remain rejected and Claims 23-26, 28 and 35 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record that were not previously applied to Claims 23-26, 28 and 35.

*A. Claims 23-26, 28, 35 and 37-39 - "**one or more compounds**"*

The limitation of "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23 is said to lack written description. The number of sugars (sucrose, fructose, glucose, galactose, maltose) and the number of PEI derivatives (sucrosylated, glycosylated, mannosylated, as well as any other derivative of PEI) are numerous. Therefore, the Examiner takes the position that the phrase encompasses innumerable combinations of sugars, PEI and PEI derivatives.

Claim 23 of the preliminary amendment filed 2-21-02 admittedly contemplates using "sugars, polyethylenimine, and polyethylenimine derivatives, and mixtures thereof". However, the Examiner takes the position that this is the only place in the specification that describes "one or more compounds" as claimed. The Examiner states that Pg 15, lines 6-8, contemplates using PEI, specifically modified PEI, more specifically sugar modified PEI, to target the mannose receptor. The Examiner takes the position that pg 15, lines 6-8, does not teach or suggest using one or more sugar, PEI or PEI derivative as claimed. Pg 15, lines 16-17, is said to teach the mannose receptor size and does not teach or suggest using Example 10 [sic] and Table 2 teaches:

> "Experimental results depicted in Table 2 provided evidence that a sugar-DNA complex, in the absence of PEI-man, can transduce Langerhans cells in vivo. Sugar complexed DNA in the absence of PEI is more efficient for use in both subcutaneous and transcutaneous methods than DNA complexed with PEI (see Table 2, experiments 3 & 5). This is a very surprising result. It shows that sugars (e.g. 8% glucose in these experiments) can also complex DNA and deliver the DNA to the Langerhans cells via the mannose receptor. Importantly, the most efficient gene delivery in vivo to the Langerhans cells was the sugar complexed DNA used in the transcutaneous way." (pg 24).

Thus, the Examiner notes that Example 10 describes a sugar-DNA complex in the absence of PEI or PEI derivates. Table 2 (pg 23) is said to disclose using PEI or mannosylated PEI but is not acknowledeged to teach combining PEI or mannyosylated PEI in combination with a sugar solution despite the clear disclosure in both Example 10, quoted above ("8% glucose"). [Note: the Applicants point out that Example 10, which references accompanying table 2, further discusses results which is contained in Example 8. Example 8 discloses that these materials were formulated in 5-10% glucose solution, as mentioned in the quote above, and that 8% glucose solution was found to be optimal.] The Examiner further states that Example 10 and Table 2 do not teach or suggest using one or more sugar, PEI or PEI derivative as claimed. Thus, the Examiner takes the position that the specification does not provide written description for any specific combination of sugar, PEI and PEI derivatives.

The Examiner states that an adequate written description of a combination of elements requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the combinations themselves. It is not sufficient to state a composition comprises one or more sugar, PEI or PEI derivative able to transfect APCs in vivo because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any combination having that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method that requires using any combination of sugar, PEI and PEI derivatives that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel,* 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.,* 43 USPQ2d 1398 (CA FC, 1997)).

Response – Written Description

A. Claims 23-26, 28, 35 and 37-39 "one or more compounds"

This application discloses the use of DNA in combination with PEI, PEI modified with various sugars, including mannose, galactose and glucose (in saline solution, Experiment 6 at page 21 line 15, Table 1), and DNA alone, DNA in combination with PEI and DNA in combination with PEI modified with mannose, each combined with a sugar (formulated in glucose solution, Experiment 8, page 22, line 35 , Table 2) *in the experiments.* Applicants submit that this is sufficient support for the claimed language "DNA one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives."

B. Claims 37-39 Therapeutic Effect/Correlation of Experiments

Claims 37-39 remain rejected under written description because the specification allegedly does not adequately describe how to apply a gene delivery complex encoding an HIV protein to the skin or mucosa of an animal such that a therapeutic or prophylactic immune response against HIV is obtained - the sole disclosed purpose for transfecting APCs disclosed in the specification for reasons of record.

Note from the Applicants: This application was filed with an experiment in the text showing an immune response (CTL response) in an animal, and a Declaration made of record at least as of the date of filing showing CTL responses associated with improved ability to control viral reproduction and enhance longevity in gravely ill animals. See Evidence Appendix 3.

Breadth of the claims

Claims 37-39 require applying a gene delivery complex to the skin or mucosa of an animal, wherein the gene delivery complex comprises DNA encoding a protein from HIV (37), from a replication-defective HIV (38), or an integration-defective, replication defective HIV (39). The only described function for such a method is to induce an immune response that treats or prevents HIV infection. The specification is admitted to describe using the

method claimed to induce an immune response in a mammal (pg 20, Example 4). Inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, the sole purpose for applying a gene complex encoding an HIV protein as claimed must induce an immune response as described in Example 4 and must treat or prevent HIV as described on pg 2, lines 20-24, and pg 18, lines 2-8. While the Examiner admits that the claims do not require inducing an immune response or treating or preventing HIV, he states without citation that merely applying a gene complex encoding an HIV protein to the skin or mucosa of an animal as claimed, in and of itself, does not have a disclosed use. The Examiner concludes, accordingly, the specification must provide adequate written description for applying a gene complex encoding an HIV protein to the skin that induces an immune response capable of treating or preventing HIV.

State of the art and unpredictability of inducing an immune response capable of treating retroviral infection

The Examiner states that the state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) is said to have taught that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, the Examiner states that a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangharn of record, Nov. 29, 1997, Lancet, Vol. 350, pages1617-1621; page 1617, top of col. 1).

More specifically, Veljkovic (Vaccine, 2001, Vol. 19, pg 1855-1862) is said to have taught:

> "As was recently reported, the rgpl 20 subunit vaccine tested in HIV-negative individuals was not only not effective - participants in Phase 1:11 clinical vaccine trials who have become infected during or following immunization with the HIV-1 env had in their sera significant neutralizing antibody titers against vaccine isolates before they became infected [2,3] - but could also be dangerous [4]." (pg 1856, col. 1, first sentence of the second full paragraph)

Thus, the Examiner remarks that the immune response against an HIV gp120 vaccine is inadequate to provide a prophylactic or therapeutic effect against HIV infection. In fact, Veljkovic taught HIV could escape recognition by HIV-specific CTL because the virus undergoes mutation within weeks after infection (pg 1857, col. 1, last sentence of the first full paragraph). McMichael explicitly described this phenomenon (Annual Rev. Immunol., 1997, Vol. 15, pg 27-296; see entire article).

The Examiner states that Hanke (Immunology Letters, 1999, Vol. 66, pg 177-181) taught administering DNA encoding HIV proteins intradermally caused a CTL response (pg 178, section 2.1). It is said that Hanke did not teach the CTL response was therapeutic or prophylactic. The Examiner says that Hanke asks the question whether inducing a CTL response can protect against HIV infection and states "CTL per se cannot prevent incoming cell-free virus from infecting host T-cells. However, if there are high levels of memory CTL present in the relevant tissue or circulation and the virus "challenge" is low, CTL might clear the small number of infected cells before the virus spreads further and establishes generalized infection" (pg 180, col. 1, Section 4.2).

The Examiner says that Weber (Eur. J. Clin. Microbiol. Infect. Dis., Nov. 2001, Vol. 20, pg 800-803) described the phase I clinical trial using plasmid encoding HIV-1 gp160 to treat HIVinfected humans. "Even though both trials were designed as phase I

clinical trials, with special focus on safety, preliminary data suggest that vaccination with the present HIV-1 DNA construct did not show any virological or immunological efficacy, which is in contrast to findings in the chimpanzee model" (pg 802, col. 2, first sentence of first full paragraph). Thus, plasmid DNA encoding gp160 does not have a therapeutic effect in humans and using DNA encoding HIV proteins in primate models does not correlate to expected results in humans.

The Examiner says that Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). For example, a canarypox vaccine failed induce a powerful enough immune response (sentence bridging columns 1 and 2). In another trial, three or four monkeys treated with a promising DNA vaccine have died due to viral breakthrough (column 2, first full sentence).

The Examiner says that Lori (Current Medical and Chemical Anti-infective Agents, 2004, Vol. 3, pg 31-41) taught that inducing an HIV-specific immune response in vivo against HIV protein fails to provide a therapeutic or prophylactic effect (pg 31, col.1, 2nd ¶, lines 7-10). *Note: this statement is false. The cite in the article is to a discussion of the AIDSVAX B/B trial, and it states as follows: "The desired phenotypical endpoint of this clinical trial was the production of protective neutralizing* ***antibodies****. Unfortunately, the analysis of the date from this trial did not indicate a significant reduction in overall infection rates based on the production of protective HIV specific* ***antibodies****." This is an example of failure of others. The reference says "our DC targeted HIV vaccine, DermaVir, a topical, therapeutic vaccine that has demonstrated immunological and clinical benefits in rhesus macaques" at page 32, Column 1, 1st full para, lines 1-5 up. The article presents pre-clinical studies, page 38-39, a theoretical basis to explain why the vaccine differs from other vaccines and its advantages over others (page 39, 2nd and 3rd full parsa) and a suggestion for its treatment as a new antiretroviral approach complementary to that of various drug classes (page 39, paragraph bridging Cols 1 and 2).*

The Examiner says that Dong (J. Exp. Med., Dec. 20, 2004, Vol. 200, No. 12, pg 1547-1557) taught, "HIV-specific cytotoxic T lymphocytes (CTL) are important in controlling HIV replication, but the magnitude of the CTL response does not predict clinical outcome" (first sentence of abstract, emphasis added). The CTL response generated against HIV-1 proteins has no correlation with either the magnitude/breadth of the response or the plasma viral load (pg 1547, col. 2, first full sentence). In other words, obtaining a CTL response against HIV proteins does not predict the clinical response.

Teachings in the specification

The Examiner admits that the applicants taught using the LW/int- plasmid encoding replication-defective, integrase-defective retroviral DNA in the claimed invention (pg 13, lines 26-37; and that replication-defective, integrase-defective retroviral DNA was described in related application 08/803,484).

The Examiner admits that Example 4 teaches transfecting dendritic cells in vitro with the LW/Int- plasmid and injecting the dendritic cells into monkeys (split subcutaneously and intravenously). One monkey showed a CTL response (pg 20, lines 8-19).

The Examiner admits that Example 9 teaches applying a gene delivery complex encoding GFP to th [sic: presumed to be "the skin"] of mice. The Examiner admits that GFP protein was expressed in dendritic cells.

The Examiner admits the specification described plasmids encoding replication-defective, integrase-defective HIV as described in application 08/989,301 (pg 18, line 30-32). In application 08/939,301, applicants call such retroviruses "Class 4" viruses that are infectious but replication-defective (pg 15, lines 1-5). In application '301, applicants teach that replication-defective HIV may fail to elicit a prophylactic immune response because it fails to replicate at all; however, replication-defective HIV may cause HIV because it replicates albeit poorly (pg 3, line 17 through pg 4, line 3). The Examiner states incorrectly, that Application '301 describes applicants' attempted to find a vector encoding a replication-defective HIV that replicated poorly so that it would elicit a prophylactic immune response without causing HIV syndrome. '301 taught numerous HIV vectors that had decreased replication and some that induced an immune response against HIV, but'301 did not teach any HIV vectors that induced a therapeutic or prophylactic immune response against HIV.

Rejection

The Examiner states that the specification does not provide adequate written description for applying a gene delivery complex encoding an HIV protein to the skin or mucosa of an animal such that a therapeutic or prophylactic immune response is obtained.

The Examiner states that Example 4 does not correlate to the claimed invention because dendritic cells were transfected in vitro and because the gene delivery complex was not applied to the skin or mucosa as claimed. Furthermore, merely inducing a CTL in one monkey by administering transfected dendritic cells as described in Example 4 is not statistically significant; the observed CTL response may have been a random event and not caused by the administration of dendritic cells. Finally, inducing a CTL response against HIV in vivo as described in Example 4 is not adequate to treat or prevent HIV infection. According to Weber (cited above), DNA encoding HIV proteins may induce an immune response without treating or preventing HIV. Nowhere have applicants provided any evidence that the CTL response observed is adequate to treat or prevent HIV or that the virus does not replicate too much and cause disease. *Note: There is a Declaration of record and peer-reviewed articles by the inventors, as well as articles by others on this point.* As such, use of DNA encoding HIV proteins as described in Example 4 would not treat or prevent disease because the virus would replicate and cause disease and because the CTL response observed is inadequate to overcome HIV infection.

Example 9, pg 23-24, is said to not correlate to the invention as now claimed because it does not disclose delivering DNA encoding HIV proteins to the skin, inducing an immune response against the proteins, specifically a therapeutic or prophylactic immune response.

Applicants appear to be attempting to find how to apply DNA encoding an HIV protein to the skin or mucosa of an animal such that a therapeutic or prophylactic immune response is obtained. Claiming a method that may exist, in the absence of knowledge as to the specific structure of the material used or the specific route of administration, dosage and immune response required to treat or prevent disease, is not a description of that method. Thus, claiming a method of using DNA encoding replication-defective retroviral proteins without defining the parameters required to induce an immune response that is therapeutic or prophylactic, i.e. the combination of PEI, sugars and PEI derivatives, specific route of administration, dosage or immune response required to treat or prevent HIV is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993) and Regents of the Univ. Calif v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)).

Examiner's comments on the Applicants' arguments

Applicants argue the language was approved in the parent application; therefore, applicants conclude the language has written description. Applicants' argument is not persuasive. The parent application claims a gene delivery complex while the instant claims require applying a gene delivery complex comprising DNA encoding an HIV protein and sugars, PEI, PEI derivatives or mixtures thereof to the skin of an animal. The instant application lacks written description for treating or preventing HIV using the methods of claims 37-39, the sole disclosed use of the methods of claims 37-39. The gene delivery complex claimed in the parent application was not solely used to treat or prevent HIV.

Applicants argue the claimed material was used in an experiment that resulted in a therapeutic effect on pg 20, Example 4. Applicants' argument is not persuasive. Example 4 does not use the claimed material; Example 4 injected dendritic cells transfected in vitro while the claims require applying a gene delivery complex to the skin or mucosa of an animal. Furthermore, obtaining a CTL response against HIV as taught in Example 4 is not predictive of the clinical outcome (Dong cited above). Accordingly, Example 4 does not correlate to the claims and does not provide a reasonable explanation that the CTL response observed would cause a therapeutic outcome.

Applicants point to Example 9, pg 23-24, which describes applying a gene complex to the skin of an animal. Applicants conclude claims 37-39 have written description because Example 9 shows a gene complex applied to the skin transfected dendritic cells. Applicants' argument is not persuasive. It is noted that Examples 8 and 9 do not teach how the DNA was applied to the skin of the mice (i.e. topically or intradermally), which may be essential to the invention. More importantly, Example 9 does not disclose delivering DNA encoding HIV proteins, or inducing a CTL response, specifically a therapeutic or prophylactic response. Thus, Example 9 does not provide correlate to the claims and does not teach treating or preventing HIV.

Applicants argue Lisziewicz (J. Invest. Derm.) details the use of the present invention to produce a CTL response. It is noted that Lisziewicz (2004) provided by applicants appears to be a copy of the article from the publisher. The correct citation for the article is J. Invest. Derm., Jan. 2005, Vol. 124, No. 1, pg 160-169, hereby referred to as Lisziewicz (2005).

Applicants argument is not persuasive because the specific combination of DNA, PEI-mannose and glucose described by Lisziewicz (2005) does not have written description in the specification as originally filed, because the narrow limitation of applying DNA, PEI-mannose and glucose topically as described by Lisziewicz (2005) does not provide adequate written description for the claim as broadly written and because Lisziewicz (2005) did not teach the CTL response was therapeutic or prophylactic.

Lisziewicz (2005) taught using DermaVir to make particles containing DNA, PElm and glucose and administering the complex on about 40 cm2 skin at four locations: the left and right upper inguinal region and left and right axillary region for 30 minutes (pg 167, col. 1, "Topical and ex vivo DermaVir immunization"). The structure of DermaVir is described as being "formulated to make a approximately 100 nm particle containing DNA, PElm, and glucose" (pg 167, col. 1, "Topical and ex vivo DermaVir Immunization" of Lisziewicz (2005)). The specific structure of DermaVir is not described. Furthermore, the combination of DNA, PElm and glucose described by Lisziewicz (2005) does not have written description in the instant specification. While the preliminary amendment contemplates using sugars, PEI, PEI derivatives or mixtures thereof (claim 23), the

specification as originally filed does not contemplate the specific combination of DNA, PEI-mannose and glucose. Given the innumerable combinations of sugars, PEI and PEI derivatives, the specification as originally filed does not reasonably lead those of skill to the conclusion that applicants contemplated the specific combination of DNA, PEI-mannose and glucose as described by Lisziewicz (2005). Accordingly, the teachings of Lisziewicz (2005) cannot be relied upon for written description.

Furthermore, Lisziewicz (2005) is limited to gene delivery particles containing plasmid DNA, PEI-mannose and glucose applied topically (pg 166, col. 2, 1st full ¶ which cannot be relied upon for written description of the gene delivery complex as broadly claimed or to applying the complex to the skin or mucosa as broadly claimed.

Finally, Lisziewicz (2005) induced CD4 helper and CD8 cells but did not obtain a therapeutic or prophylactic effect against HIV. However, Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Furthermore, obtaining a CTL response against HIV as taught in Lisziewicz (2005) is not predictive of the clinical outcome (Dong cited above). Finally, Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41), one of the inventors in the instant application, taught that inducing HIV-specific antibodies failed to provide a protective effect (pg 31, col. 1, 2nd ¶, lines7-10). Lori also says inducing a cellular immune response will not prevent H IV infection (pg 31, col. 2, first sentence of the new paragraph). While Lori suggests a cellular immune response may treat HIV in the same sentence, Lori does not teach the CTL response required to do so. Applicants have not provided any evidence or any reasonable expectation that CD4 and CD8 cells that recognize HIV proteins overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained. [sic] Without such guidance, merely inducing CD4 helper and CD8 cells that recognize HIV proteins as described by Lisziewicz (2005) is not adequate written description for inducing an immune response against HIV proteins that is therapeutic or prophylactic.

As such, Lisziewicz (2005) cannot be relied upon for written description of the instant application because it required combining DNA, PElm and glucose, which does not have written description in the instant application, because neither the instant application or Lisziewicz (2005) disclose the structure of DermaVir and because inducing CD4 and CD8 response against HIV does not induce a therapeutic or prophylactic effect against HIV.

Applicants' arguments on pg 10 titled "Fine-tuned DNA" are noted; however, the arguments are not persuasive. The examiner has not required any fine-tuning of gene complexes disclosed in the specification or known in the art. The examiner has required a reasonable written description of a gene complex that will induce a therapeutic or prophylactic immune response against HIV upon being administered to the skin as claimed.

Applicants argue Lisziewicz (2001, J. Virol., Aug 2001, Vol. 75, No. 16, pg 7621-7628) provides written description for treating or preventing HIV using DNA encoding HIV proteins as claimed. [Not true. This article was properly submitted to provide support for assertions in the application that the Examiner, according to the explicit instructions in a cited MPEP section, should credit] Applicants argument is not persuasive. Lisziewicz (2110) transfected dendritic cells with a vector encoding HIV proteins, injected them subcutaneously into monkeys and obtained a CTL response against HIV (pg 7622, col. 2, first two paragraphs; pg 7652, Fig. 6b). First, Lisziewicz 2001) does not correlate to the claims because the gene delivery complex was not applied to the skin or mucosa as claimed. Second, the vector used by Lisziewicz (2001) was not described in the specification as originally filed. The vector used by Lisziewicz (2001) has six stop codons, one deletion in

the pol region, one stop codon and one deletion in the second reading frame and is integrase negative (pg 7621, col. 2). While pg 18, line 31, of the instant application mentions the LWint- vector of application 08/803484, the LWint vector does not have six stop codons, one deletion in the pol region, one stop codon and one deletion in the second reading frame and is integrase negative. Therefore, the vector in Lisziewicz (2001) does not have written description in the specification as originally filed. Third, Lisziewicz (2001) did not obtain a CTL response capable of treating or preventing HIV. The art taught that inducing an HIV-specific immune response in vivo against HIV protein failed to provide a therapeutic or prophylactic effect (Lori, Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41; pg 31, col. 1, 2 nd ¶, lines 7-10). Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Applicants have not provided any evidence or any reasonable explanation that the CTL response against HIV obtained in Lisziewicz (2001) overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained. Without such guidance, inducing a CTIL response against HIV in vivo as described by Lisziewicz (2001) is not adequate written description for inducing a therapeutic or Prophylactic CTL response against HIV in vivo.

It is noted that Lisziewicz (2005) states DermaVir was used in Lisziewicz (2001, of record); however, Lisziewicz (2001) does not discuss using DermaVir. Lisziewicz (2001) described using PEI or PEI-mannose to deliver DNA (at a 5:1 ratio) without using glucose. The gene delivery complex used in Lisziewicz (2005) is different than the one used in Lisziewicz (2001).

Response – Written Description

B. Therapeutic Effect/Correlation of Experiments

It is noted that Claims 23-26, 28, 30-33, 35 and 40-43 are not subject to this rejection. The specification is admitted to describe using the method claimed to induce an immune response in an animal; it is admitted that claimed materials were described, and that transfection has been demonstrated; and it is also admitted that the claims do not require inducing an immune response or treating or preventing HIV.

Thus the question is whether the examiner's requirement for a further demonstration of a therapeutic response is appropriate, and if appropriate, whether this additional burden has been met by the text of the application, and in addition, by copious, peer-reviewed data submitted by the applicant, and the approval of this vaccine by the FDA for clinical trial.

The written description requirement relates to whether the claimed subject matter was described in the application (MPEP 2163). A description as filed is presumed to be adequate (MPEP 2163.04) The burden on the Examiner is found in MPEP 2163.04 I:

(A) Identify the Claim Limitation at issue.

(B) Establish a prima facie case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the

inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description.

upon reply, MPEP 2163.04 II states that the Examiner has specific responsibility:

Upon reply by applicant, before repeating any rejection under 35 U.S.C. 112, para. 1, for lack of written description, review the basis for the rejection in view of the record as a whole, including amendments, arguments, and any evidence submitted by applicant. If the whole record now demonstrates that the written description requirement is satisfied, *do not repeat the rejection in the next Office action.* (emphasis added)

The text and the experimental results submitted by the applicants are entitled to a reasonable amount of credit: MPEP 707.07(l) provides:

> The results of the tests and examples should not normally be questioned by the examiner unless there is reasonable basis for questioning the results. If the examiner questions the results.... The applicant must reply to the rejection, for example, by providing the results of an actual test or example which has been conducted, or by providing relevant arguments that there is strong reason to believe that the result would be as predicted.

In the present case, criterion A is not met, because there is no claim limitation in issue. The Examiner has admitted the claimed method has been described, and that the various materials used in the method and mentioned in the application have been used to transfect cells and raise an immune response in examples in the application. The Examiner has objected however, that the art was and is unpredictable, that the examples don't correlate with the claimed invention, and that neither the inventors' proffer of affidavits, nor peer-reviewed articles supporting the statements in the application, nor notice of a decision by the FDA to allow clinical trial of the claimed invention is sufficient to overcome his objections.

The Claimed invention is:

A method of transfecting antigen presenting cells, the steps comprising

selecting a gene delivery complex that targets antigen presenting cells, comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives,

and applying the complex to the skin or mucosa surfaces of an animal,

wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter. This method is acknowledged to find support in the application. The question raised by the Examiner is whether the specification supports the further limitations, wherein the protein is from a human immunodeficiency virus (Claim 37); that is replication-defective (38); by virtue of being integration-defective.

1. The Claim Language was approved in the Parent Application.

It is further noted that the present application is a division of USPN 6,420,176, re Composition for Delivering DNA into Antigen Presenting Cells, which has the same specification as the present application, and includes the following dependent Claims (copy enclosed at Evidence Appendix – 1):

> 3. The gene delivery complex of Claim 2, wherein the reverse transcriptase-dependent virus is *a human immunodeficiency virus.*
> 4. The gene delivery complex of Claim 3, wherein the human immunodeficiency virus is *replication-defective.*
> 5. The gene delivery complex of claim 3, wherein the human immunodeficiency virus is *integration-defective.*

In an effort to expedite prosecution, the limitations with respect to the material used in the present claimed method were made to quote those of the parent patent. Similar limitations are also found in the parent patent, at Claims 11-13. The Applicants note that the issues involving written description and enablement were raised by the Examiner during prosecution of the parent patent and resolved at that time. The Applicants have a right to uniform application of the patentability standard (MPEP 706 I; MPEP 707.07(j)). Piecemeal Examination is to be avoided (MPEP 707.07(g)). Inventions relating to HIV/AIDS and cancer are specifically important, and suitable for expedited processing. (MPEP 708.02 X.) And, applications that are substantially allowable should be considered special and prompt action taken to require correction of formal matters (MPEP 1301). Even in ordinary cases, the Examiner should never overlook the importance of his or her role in allowing claims which properly define the invention (MPEP 706). The examiner's action should be constructive in nature and when possible should offer a definite suggestion for correction (MPEP 706 II).

The Examiner has admitted that the claimed method meets the written description requirements, and the objections with respect to written description relate back to language that was considered and allowed in the parent patent.

2. The Claimed Material was used in an Experiment in the Application, and produced a Therapeutic Result, which has been confirmed by Subsequent, Peer-Reviewed Publication.

The claimed function of the method is to transfect antigen presenting cells. The Examiner has acknowledged that transfection of antigen presenting cells has been demonstrated, and has acknowledged that a CTL response was obtained.

The Examiner has made a requirement for a further showing of a therapeutic or prophylactic effect using a subset of materials. The Applicants have pointed to Example 4, page 20, which discloses that an immune response, that is, a CTL response, had been obtained in at least one animal after a single immunization attempt, using a LW/Int- plasmid (disclosed at page 18, lines 30-31 as a plasmid DNA encoding an integration and replication defective HIV). That immune response is evidence that the claimed effect, transfection of antigen presenting cells, has been achieved, and further that the stated purpose of transfection using the described embodiment, to raise an immune (CTL) response, has been achieved.

The application discloses that CTL responses are associated with therapeutic effects at page 4, lines 7-11: "Expression of foreign genes in antigen presenting cells (APC) may be used to generate efficient CTL response in animals. Therefore, gene transfer and genetic modification of APC has the potential to generate effective vaccine and therapeutic approaches ...." That is, generation of a CTL response is a legitimate marker for a therapeutic effect.

The Examiner states that Example 4 does not correlate with the claimed invention, however, because Example 4 does not use the claimed method of delivery of genes through the skin. However, the Applicants point out that Example 4 was included to show efficacy of the claimed materials in a more classical method, such as described in USSN 08/803,484 (incorporated by reference and enclosed at Evidence Appendix – 2). The application discloses in the discussion at the end of Example 9 that

> These experiments show that PEI-(Man)-DNA complexes are able to penetrate in the skin, and deliver the DNA into Langerhans cells. The Langerhans cells were activated and migrated into the draining LN and expressed genes encoded by the DNA construct in the LN. It is known that cultured DC reinjected to the body migrate in the LN and generate efficient immune response. This invention demonstrates that in vitro isolation of DC is not required to transfer genes into Langerhans cells, or for gene expression in the lymphoid organs. We have also demonstrated that expression of a replication defective virus in DC results in efficient induction of a CTL response in vitro and in vivo (see above *sic*: This is a reference to Example 4). Therefore, we have shown that transcutaneous gene delivery with complexes (like PEI-man-DNA) can be utilized to generate immune responses against proteins encoded in the DNA.

Further, the Applicants have submitted an article by the inventors from a peer-reviewed journal, Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/Aids" J

Invest Dermatol, 2004 detailing the use of the present invention to produce CTL responses (Enclosed at Evidence Appendix 4). That article begins as follows:

> "One strategy for a new immunotherapeutic intervention against human immunodeficiency virus (HIV) infection is to develop a vaccine that can reconstitute HIV-specific immunity, thereby improving the efficacy of the present antiretroviral regimens. The therapeutic efficacy of such a vaccine would be mediated by HIV-specific T cells...."

This article is consistent with the teachings of the present application, and its acceptance for publication is some evidence that others of skill in the relevant art agree with the inventors that the CTL response is an acceptable marker for a therapeutic response. This article also includes a detailed discussion of a comparison between the immune responses raised via topical immunization and *ex vivo* immunization. The entire discussion revolves around T cell responses. See page 6, Col. 1. The authors conclude at page 7, first full paragraph, lines 1-3 that "We have shown here in a primate model that topical DermaVir vaccination is comparable with *ex vivo* DC-based vaccination." This article confirms the results disclosed in the present application, and is some evidence that those of skill in the art accept the results shown in the present application.

Yet another article consistent with the teachings of this application is Lori (Current Medical and Chemical Anti-infective Agents, 2004, Vol. 3, pg 31-41) (Evidence Appendix 7), which discusses the present invention, which has been shown to be of value as a treatment for existing viral infection. This reference has been cited by the Examiner as teaching that an HIV-specific immune response in vivo against HIV protein fails to provide a therapeutic or prophylactic effect (pg 31, col.1, 2nd ¶, lines 7-10), and the Examiner claims that this result must necessarily be extended to the present invention. This reference demonstrates the failure of others. The passage cited by the Examiner states in full:

> "The desired phenotypical endpoint of this clinical trial was the production of protective neutralizing **antibodies**. Unfortunately, the analysis of the date from this trial did not indicate a significant reduction in overall infection rates based on the production of protective HIV specific **antibodies**." (emphasis added)

What the reference says about the present invention is "our DC targeted HIV vaccine, DermaVir, a topical, therapeutic vaccine that has demonstrated immunological and clinical benefits in rhesus macaques" at page 32, Column 1, 1st full para, lines 1-5 up. The article, at pages 38-39, describes the vaccine as "(i) plasmid DNA, encoding a full-length replication and integration defective HIV, (ii) plyethylenimine-mannose (PEIm), a chemical polymer and (iii) glucose solution," (p. 38, col. 2, 1st full para.) presents pre-clinical studies, page 38-39, a theoretical basis to explain why the vaccine differs from other vaccines and its advantages over others (page 39, 2nd and 3rd full para.) and a suggestion for its treatment as

a new antiretroviral approach complementary to that of various drug classes (page 39, paragraph bridging Cols 1 and 2).

Example 4 demonstrates the efficacy of the claimed materials in the *ex vivo* method; the other examples demonstrate that the topical method works as well as or better than, the *ex vivo* method for very similar materials, except that a marker gene is used, the discussion in the disclosure ties the two materials together, and the subsequent publications demonstrate that the disclosure in the application is acceptable for publication in peer-reviewed journals.

C. The Experiments overcome the State of the Art because the predicted results are demonstrated.

The Examiner has cited a number of articles, some of which pre-date, and some of which post-date, the file date of the present application. According to the Examiner, these articles establish that state of the art prior to the making of the claimed invention was that the likelihood of inducing an immune response "capable of treating retroviral infection" was unpredictable.

While the Examiner may use whatever relevant information is at hand to establish a prima facie case questioning statements in an application, such prima facie case is overcome when the applicant can point to either text in the application, new experimental results, or argument showing that there is a strong reason to believe that the results will be as predicted. MPEP 707.07(l). In this case, the predicted results are transfection of antigen presenting cells, and the disclosed purpose for the present embodiment is to raise an immune response. The applicants have admittedly pointed to experimental results that produce the predicted result: transfection of antigen presenting cells, as shown by the raising of an immune response.

The Examiner admits that the specification describes the use of LW/int- plasmid encoding replication-defective, integrase-defective retroviral DNA in the claimed invention; and that replication-defective, integrase-defective retroviral DNA was described in related application 08/803,484); that Example 4 teaches transfecting dendritic cells in vitro with the LW/Int- plasmid and injecting the dendritic cells into monkeys (split subcutaneously and intravenously); that one monkey showed a CTL response (pg 20, lines 8-19); that Example 9 teaches applying a gene delivery complex encoding GFP to th [sic: presumed to be "the skin"] of mice, and that GFP protein was expressed in dendritic cells.

Because the Examiner has admitted that the text of the application describes the use of the claimed materials in the claimed invention, and acknowledges the proffered

experiments yield the predicted results (transfection of cells; immune response) the Examiner has admitted that the invention is described in the application.

To the extent that the Examiner has questioned whether the admittedly described invention will actually enable anyone to treat a specific disease, his arguments are more properly related to the enablement requirement. The Examiner has repeated these arguments in an enablement rejection that is discussed below.

3. Enablement

The rejection of claims 23-26, 28, 30-33, 35 and 40-42 regarding obtaining a therapeutic effect by applying a gene delivery complex encoding at least one immunogen,ic antigen to the skin or mucosa of an animal was withdrawn in the office action of 10-5-05.

Claims 37-39 remain rejected under 35 U. S.C. 112, first paragraph, because they are said to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Claims 37-39 are said not to be enabled because the specification does not provide adequate guidance for one of skill to induce a therapeutic or prophylactic immune response by applying a gene delivery complex encoding HIV to the skin or mucosa of an animal.

Breadth of the Claims

Claims 37-39 are said to require applying a gene delivery complex to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding an immunogenic protein operably linked to a promoter; and ii) sugar, polyethylenimine (PEI), a PEI derivative, wherein the protein is from HIV (37), a replication-defective HIV (38), or an integration-defective, replication-defective HIV (39).

The specification is admitted to describe using the method claimed to induce an immune response in a mammal (pg 20, Example 4). However, the Examiner takes the position that merely inducing an immune response in a mammal, in and of itself, does not have an enabled use because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, inducing an immune response against HIV according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. The ordinary artisan reading claims 37-39 in view of the specification would determine that the immune response against HIV protein must be therapeutic or prophylactic. Enablement rejection b) is based on the sole disclosed use for the methods of claims 37-39.

Note from the Applicants: This application was filed with an experiment in the text showing an immune response (CTL response) in an animal, and a Declaration made of record at least as of the date of filing showing CTL responses associated with improved ability to control viral reproduction and enhance longevity in gravely ill animals. See Evidence Appendix 3.

State of the art and unpredictability of inducing an immune response capable of treating retroviral infection

The state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) teaches that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangharn of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

More specifically, Veljkovic (Vaccine, 2001, Vol. 19, pg 1855-1862) taught:

"As was recently reported, the rgpl20 subunit vaccine tested in HIV-negative individuals was not only not effective - participants in Phase 1:11 clinical vaccine trials who have become infected during or following immunization with the HIV-1 env had in their sera significant neutralizing antibody titers against vaccine isolates before they became infected [2,3] - but could also be dangerous [4]." (pg 1856, col. 1, first sentence of the second full paragraph)

Thus, the Examiner states that the immune response against an HIV gp120 vaccine is inadequate to provide a prophylactic or therapeutic effect against HIV infection.

The Examiner adds that, in fact, Veljkovic taught HIV could escape recognition by HIV-specific CTL because the virus undergoes mutation within weeks after infection (pg 1857, col. 1, last sentence of the first full paragraph). McMichael explicitly described this phenomenon (Annual Rev. Immunol., 1997, Vol. 15, pg 27-296; see entire article).

The Examiner points to another paper, Hanke, (Immunology Letters, 1999, Vol. 66, pg 177-181) saying that it taught administering DNA encoding HIV proteins intradermally caused a CTL response (pg 178, section 2.1). The Examiner states that Hanke did not teach the CTL response was therapeutic or prophylactic. The Examiner says that Hanke asks the question whether inducing a CTL response can protect against HIV infection and states "CTL per se cannot prevent incoming cell-free virus from infecting host T-cells. However, if there are high levels of memory CTL present in the relevant tissue or circulation and the virus 'challenge" is low, CTL might clear the small number of infected cells before the virus spreads further and establishes generalized infection" (pg 180, col. 1, Section 4.2).

Weber (Eur. J. Clin. Microbiol. Infect. Dis., Nov. 2001, Vol. 20, pg 800-803) described the phase I clinical trial using plasmid encoding HIV-1 gp160 to treat HIV-infected humans. "Even though both trials were designed as phase I clinical trials, with special focus on safety, preliminary data suggest that vaccination with the present HIV-1 DNA construct did not show any virological or immunological efficacy, which is in contrast to findings in the chimpanzee model" (pg 802, col. 2, first sentence of first full paragraph). Thus, plasmid DNA encoding gp160 does not have a therapeutic effect in humans and using DNA encoding HIV proteins in primate models does not correlate to expected results in humans.

Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). For example, a canarypox vaccine failed to induce a powerful enough immune response (sentence bridging columns I and 2). In another trial, three or four monkeys

treated with a promising DNA vaccine have died due to viral breakthrough (column 2, first full sentence).

Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41) taught that inducing an HIV-specific immune response in vivo against HIV protein fails to provide a therapeutic or prophylactic effect (pg 31, col. 1, 2 nd ¶, lines 7-10). *Note: the Applicants note this portion of the reference was discussing the AIDSVAX B/B vaccine which was primarily devoted to promoting an antibody response, and demonstrates failure of others. With respect to the presently claimed invention, the reference says "our DC targeted HIV vaccine, DermaVir, a topical, therapeutic vaccine that has demonstrated immunological and clinical benefits in rhesus macaques" at page 32, Column 1, 1st full para, lines 1-5 up. The article presents pre-clinical studies, page 38-39, a theoretical basis to explain why the vaccine differs from other vaccines (page 39, 2nd full para) and a suggestion for its treatment as a new antiretroviral approach complementary to that of various drug classes (page 39, paragraph bridging Cols 1 and 2).*

Dong (J. Exp. Med., Dec. 20, 2004, Vol. 200, No. 12, pg 1547-1557) taught, "HIV-specific cytotoxic T lymphocytes (CTL) are important in controlling HIV replication, but the magnitude of the CTL response does not predict clinical outcome" (first sentence of abstract, emphasis added). The CTL response generated against HIV-1 proteins has no correlation with either the magnitude/breadth of the response or the plasma viral load (pg 1547, col. 2, first full sentence). In other words, obtaining a CTL response against HIV proteins does not predict the clinical response.

Teachings in the specification

Applicants admittedly taught using the LW/int- plasmid encoding replication - defective, integrase-defective retroviral DNA in the claimed invention ((pg 13, lines26-37), described in related application 08/803,484).

Example 4 teaches transfecting dendritic cells in vitro with the LW/Int- plasmid and injecting the dendritic cells into monkeys (split subcutaneously and intravenously). One monkey showed a CTL response (pg 20, lines 8-19).

Example 9 teaches applying a gene delivery complex encoding GFP to the skin of mice. GFP was expressed in dendritic cells.

The Examiner admits that the specification teaches making plasmids encoding replication defective, integrase-defective HIV as described in application 08/989,301 (pg 18, line 30-32). In application 08/939,301, applicants call such retroviruses "Class 4" viruses that are infectious but replication-defective (pg 15, lines 1-5). In application 08/989301, applicants teach that replication defective HIV that does not replicate effectively is inadequate to elicit a protective cellular immune response. Alternatively, replication defective HIV that does replicate effectively causes disease and sometimes fatal (pg 3, line 17 through pg 4, line 3).

Therefore applicant's idea was to find an HIV vector that had enough infectivity /replication to induce a therapeutic immune response against HIV without causing HIV syndrome. 08/989301 is said to teach numerous HIV vectors that had decreased replication and some that induced an immune response to HIV, but 08/989301 did not teach any HIV vectors that induced a THERAPEUTIC or PROPHYLACTIC immune response against HIV or any HIV vectors that had enough infectivity/replication to induce a therapeutic immune response aginst HIV without causing HIV syndrome.

Rejection

Example 4 is said not to correlate to the claimed invention because dendritic cells were transfected in vitro and because the gene delivery complex was not applied to the skin or mucosa as claimed. Furthermore, merely inducing a CTL in one monkey by administering transfected dendritic cells as described in Example 4 is not statistically significant; the observed CTL response may have been a random event and not caused by the administration of dendritic cells. Finally, inducing a CTL response against HIV in vivo as described in Example 4 is not adequate to treat or prevent HIV infection. According to Weber (cited above), DNA encoding HIV proteins may induce an immune response without treating or preventing HIV. Nowhere have applicants provided any evidence that the CTL response observed is adequate to treat or prevent HIV or that the virus does not replicate too much and cause disease. As such, use of DNA encoding HIV proteins as described in Example 4 would not treat or prevent disease because the virus would replicate and cause disease and because the CTL response observed is inadequate to overcome HIV infection.

Example 9, pg 23-24, does not correlate to the claimed invention because it does not disclose delivering DNA encoding HIV proteins to the skin, inducing an immune response against the protein encoded by the DNA (GFP), or inducing a therapeutic or prophylactic immune response against HIV proteins.

The Examiner admits that the applicants' prior application, 08/989301 taught numerous HIV vectors that had decreased replication and some that induced an immune response against HIV, but 08/989301, but says that it did not teach any HIV vectors that induced a therapeutic or prophylactic immune response against HIV or any HIV vectors that had enough infectivity/replication to induce a therapeutic immune response against HIV without causing HIV syndrome. Thus, it was unknown how to use an HIV vector to obtain a theraiDeutic or Prophylactic immune response against HIV in a host.

The Examiner states that the specification does not provide adequate guidance regarding how to obtain a therapeutic or prophylactic effect by applying DNA encoding a replication defective retrovirus in an animal as claimed. The specification does not teach the amount of a cellular immune response that is therapeutic or prophylactic effect against a replication defective retrovirus. The amount of dendritic cells required to obtain adequate antigen presentation is not provided in the specification. The amount of retroviral protein expression required to obtain the desired cellular immune response is not provided in the specification. The amount of replication and infectiousness required to obtain the desired balance between therapy and pathogenicity is not provided in the specification. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine how to make and/or use a replication defective retrovirus to obtain a therapeutic/prophylactic effect without causing disease or death.

The Examiner states that, in addition, it was unpredictable what vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic or prophylactic effect using in vivo or ex vivo gene therapy (Miller 1995, FASEB J., Vol. 9, pg 190-199; pg 198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶, pg 65, 1st ¶ under Conclusion section; Verma, Sept. 1997, Nature, Vol. 389, pg 239-242; see entire article, specifically pg 240, sentence bridging col. 2 and 3; Crystal, 1995, Science, Vol. 270, pg 404-410, pg 409; Ross, Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1782, col. 2, 1st full ¶; pg 1789, col. 1, 18t ¶, all of record).

The specification is said not to enable applying DNA encoding a lentiviral protein to the skin or mucosa to transfect APCs and obtain a therapeutic or prophylactic effect. It is said that the specification does not teach that applying DNA to the mucosa results transfection of APCs or in expression of the protein in the APCs. It is said the specification does not teach the amount of lentiviral protein expression required for the APCs to present adequate antigens to the immune system such that a therapuetic/prophylactic immune response is obtained. It is said the specification does not teach the immune response to a lentiviral antigen required to treat or prevent disease. It is said the specification does not provide the combination of vector, promoter, dosage, level of expression that would result in a therapeutic/prophylactic effect. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine the vector, promoter, cell, dosage, level of expression and route of administration required to obtain a therapeutic or prophylactic effect using the method claimed.

Applicants argue numerous vectors are described in the specification; therefore, applicants conclude the claims are enabled. Applicants' argument is not persuasive. The instant application and 08/939,301 taught numerous HIV vectors that showed decreased replication and some that induced an immune response against HIV in vivo, but applicants do not teach any vectors encoding HIV proteins that induced a therapeutic or prophylactic immune response against HIV or to overcome the unpredictability in the art that the immune response obtained HIV in vivo is adequate to treat or prevent HIV.

Applicants' discussion of en re Brana is noted but is misplaced because it relates to utility and not enablement.

Applicants' discussion of the Wands factors is noted but is moot. Applicants' discussion does not set forth any error in the examiner's analysis of the claimed invention using the Wands factors in the enablement rejection.

Applicants argue the claims merely require inducing an immune response against HIV and do not require inducing an immune response against HIV that is therapeutic or prophylactic. Applicants' argument is not persuasive. Merely inducing an immune response in a mammal, in and of itself, does not have an enabled use because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, inducing an immune response against HIV according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. This interpretation is reasonable given the sole disclosed purpose of inducing an immune response against HIV in the specification as originally filed. Applicants have not pointed to any other use for inducing an immune response against HIV in vivo other than therapy or prophylaxis.

Applicants' argue use of the raw material (the gene delivery complex) is enabled (pg 19, first full paragraph). Applicants' argument is not persuasive. The claims are drawn to methods of using a gene delivery complex in vivo and are not drawn to the gene delivery complex. The methods claims are rejected under enablement because the specification does not enable those of skill to use the gene delivery in vivo to obtain an immune response against HIV that is therapeutic or prophylactic.

Applicants argue publications by the inventors confirm the statement on pg 4, lines 7-11, that expression of antigens in APCs may be used to generate efficient CTL response in vivo and has the potential to generate effective vaccine and therapeutic approaches (pg 19, second full paragraph of response). Applicants' argument is not persuasive. Lisziewicz (2001) and Lisziewicz (2005) cannot bb relied upon for enablement of the claims because

Lisziewicz (2005) required combining DNA, PlElm and glucose, which was not disclosed in the instant application, because Lisziewicz (2001) taught a vector not described in the instant application, because neither the instant application or Lisziewicz (2005) disclosed the structure of DermaVir and because inducing an immune response against HIV as described in both references does not overcome the unpredictability in the art regarding how to induce an immune response against HIV that is therapeutic or prophylactic.

Applicants argue the specification does not have to set forth what the "prior art predicted to be needed." Applicants argue the specification taught the details of basic research into the physiological mechanisms of the CTL response of HIV, advances in new materials, a theoretical and practical basis for targeting APCs and a method of vaccinating. Applicants' arguments are not persuasive. The specification does not teach how to perform any basic research into the physiological mechanisms of raising a CTL response against HIV. The only disclosed use for inducing a CTL response against HIV is for treatment or prophylaxis (pg 2, lines 20-24; pg 18, lines 2-8). The specification does not teach how to overcome the unpredictability in the art by teaching how to induce a CTL response against HIV in vivo that is therapeutic or prophylactic.

Applicants' argue plasmids encoding replication-defective HIV are not the same as replication-defective retrovirus particles (pg 20, first paragraph). *note: experimental data ignored.* Applicants' argument is not persuasive. While plasmids and retroviral particles encoding HIV proteins were known in the art to induce an immune response against HIV in vivo, no plasmids or retroviral particles were known in the art to induce an immune response against HIV in vivo that was therapeutic or prophylactic. Applicants have not overcome the unpredictability in the art by teaching how to obtain an immune response against HIV in vivo that is therapeutic or prophylactic.

Applicants argue Lisziewicz (2001) taught using plasmid LW/int- and refers to US application 08/803484 in Example 1 (pg 18, line 31) of the instant application. Therefore, applicants' conclude Lisziewicz (2001) correlates to the claimed invention. Applicants' argument is not persuasive. The instant application does not teach the structure of the LW/int- plasmid. While application '484 taught numerous vectors, '484 did not mention the LW/int- vector or describe any vector having six stop codons, one deletion in the pol region, one stop codon and one deletion in the second reading frame and is integrase negative as described in Lisziewicz (2001). *Note: mischaracterization of earlier application.* Therefore, the reference on pg 18, line 31, to application 08/803484 is not enabling for those of skill to make the LW/int- vector. Furthermore, Lisziewicz (2001) did not obtain a CTL response capable of treating or preventing HIV. It was known that inducing an HIV-specific immune response in vivo against HIV protein failed to provide a therapeutic or prophylactic effect (Lori and Ready, both cited above). Applicants have not provided any evidence or any reasonable explanation that the CTL response against HIV obtained in Lisziewicz (2001) overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained.

Applicants argue Lisziewicz (J. Invest. Derm.) details the use of the present invention to produce a CTL response. It is noted that Lisziewicz (2004) provided by applicants appears to be a copy of the article from the publisher. The correct citation for the article is J. Invest. Derm., Jan. 2005, Vol. 124, No. 1, pg 160-169, hereby referred to as Lisziewicz (2005).

Applicants argument is not persuasive because the specific combination of DNA, PEI-mannose and glucose described by Lisziewicz (2005) does not have support in the specification as originally filed, because the narrow limitation of applying DNA, PEImannose and glucose topically as described by Lisziewicz (2005) does not enable the

combination of elements as broadly written and because Lisziewicz (2005) did not teach the CTL response was therapeutic or prophylactic.

Lisziewicz (2005) taught using DermaVir to make particles containing DNA, PElm and glucose and administering the complex on about 40 cm^2 skin at four locations: the left and right upper inguinal region and left and right axillary region for 30 minutes (pg 167, col. 1, "Topical and ex vivo DermaVir immunization"). The structure of DermaVir is described as being "formulated to make a approximately 100 nm particle containing DNA, PElm, and glucose" (pg 167, col. 1, "Topical and ex vivo DermaVir Immunization" of Lisziewicz (2005)). The specific structure of DermaVir is not described. Furthermore, the combination of DNA, PElm and glucose described by Lisziewicz (2005) does not have support in the instant specification. While the preliminary amendment contemplates using sugars, PEl, PEl derivatives or mixtures thereof (claim 23), the specification as originally filed does not contemplete the specific combination of DNA, PEI-mannose and glucose. Given the innumerable combinations of sugars, PEl and PEl derivatives, the specification as originally filed does not reasonably lead those of skill to the conclusion that applicants contemplated the specific combination of DNA, PEI-mannose and glucose as described by Lisziewicz (2005). Accordingly, the teachings of Lisziewicz (2005) cannot be relied upon for enablement.

Furthermore, Lisziewicz (2005) is limited to gene delivery particles containing plasmid DNA, PEl-man nose and glucose applied topically (pg 166, col. 2, 1st full ¶, which cannot be relied upon for enablement of the gene delivery complex described in the instant application or to applying the complex to the skin or mucosa as now claimed.

Finally, Lisziewicz (2005) induced CD4 helper and CDS cells but did not obtain a therapeutic or prophylactic effect against HIV. However, Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such e vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Furthermore, obtaining a CTL response against HIV as taught in Lisziewicz (2005) is not predictive the clinical outcome (Dong cited above). Finally, Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41), one of the inventors in the instant application, taught that inducing HIV-specific *antibodies* [emphasis added] failed to provide a protective effect (pg 31, col. 1, 2 d T, lines7-10). Lori also says inducing a cellular immune response will not prevent HIV infection (pg 31, col. 2, first sentence of the new paragraph). [sic: the applicants note that therapeutic vaccination cannot prevent infection because it is administered after infection has occurred.] While Lori suggests a cellular immune response may treat HIV in the same sentence, Lori does not teach the CTL response required to do so. Applicants have not provided any evidence or any reasonable expectation that CD4 and CD8 cells that recognize HIV proteins overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained. Without such guidance, merely inducing CD4 helper and CD8 cells that recognize HIV proteins as described by Lisziewicz (2005) is not adequate to enable inducing an immune response against HIV proteins that is therapeutic or prophylactic.

As such, Lisziewicz (2005) cannot be relied upon for enablement of the instant application because it required combining DNA, PElm and glucose, which does not have support in the instant application, because neither the instant application or Lisziewicz (2005) disclose the structure of DermaVir and because inducing a CD4 and CD8 response against HIV does not induce a therapeutic or prophylactic effect against HIV.

Response

This application includes information about multiple non-viral delivery vectors (the claimed complex comprising DNA and one or more compounds selected from the group consisting of sugars, PEI and PEI derivatives, and the experiments contain a clear description of the materials that were used, including the promoters (Example 1, page 19, line 9 and Example 2, page 19 line 18). Level of expression is reported in Example 1 page 19, lines 3-10, Example 2, lines 21-22, Example 3, Fig. 5 (as CTL in vivo response), Example 5 line 26, Example 6, Table 1, Example 7, lines 23-26, Example 8, Table 2. Different routes of administration were used in Example 4 (injection) and Example 8 (topical).

Response – Enablement

The applicants note that the present rejection lies against Claims 37-39. Claims 23-26, 28, 30-33, 35 and 40-43 are admittedly enabled. This is essentially the same rejection as the Written Description rejection above, and many of the same arguments apply. For the sake of brevity and clarity, the argument with respect to written description above has been limited to the extent possible to the underlying facts. That is, to a discussion of the words and evidence relating to the Written Description requirement. In sum, the Applicants have, above, pointed out that the Claims are supported by specific teachings in the application text and by experimental results, and the teachings of the application have been confirmed by subsequent work of both the authors and others. The teachings of the application have been accepted by peer-reviewed journals. What follows is a discussion of the law applicable to the legal question of enablement, and an analysis of the law applied to the present case.

A. Applicable law: 35 USC § 101 and § 112 – Utility, Enablement, Written Description

The Examiner has stated that the Applicants have not cited applicable or controlling law. The Examiner attempts to avoid the applicable precedent by characterizing the present rejection as relating to "utility and not enablement." Upon further review, the applicants note that the statement of law previously supplied is correct. The controlling case law remains *In re Brana*, 51 F.3d 1560, 34 USPQ 2d 1436 (Fed. Cir. 1995), where the Federal Circuit reversed a decision by the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board) affirming an Examiner's rejections of claims to antitumor compounds for failure to comply with 35 USC §112, 1st ¶.

In re Brana was decided in 1995. At the time the Federal Circuit observed that the question of what an applicant must prove with respect to the utility of pharmaceutical preparations had been settled by the case law, citing cases in its predecessor court that went

back to 1961 (*id* at 51 F.3d 1560, 1564). The Court also noted that the utility requirement is found in 35 USC § 101, but that the requirement is subsumed in the written description requirement (*id*). This means that when the issue of utility is involved, cases decided under the headings "written description," "enablement," "utility," 35 USC § 101, and 35 USC § 112 may be relevant, and certainly cannot be distinguished on the basis of the heading alone.

One of the issues in the *In re Brana* case was whether the applicants proved the claimed compounds useful (*id*, at 1566). That is, whether the tests offered by the applicants to prove utility were inadequate to convince one of ordinary skill in the art that the claimed compounds were useful *as antitumor agents*. The Applicants had pointed to language in the application, and *in vitro* data in the application. The Examiner had pointed to journal articles discussing the therapeutic predictive value of *in vivo* murine tests. The Applicants pointed to a Declaration filed during prosecution with *in vivo* animal data (murine models).

The Court ruled that *the applicants should not have been required to substantiate their presumptively correct disclosure* to avoid a rejection under the first paragraph of § 112, and that the later-filed Declaration was available to prove assertions made in the patent application (*id* at 1567).

The Court specifically addressed the question of whether animal models can be used to demonstrate utility, and commented as follows: "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, *even though it may eventually appear that the compound is without value in the treatment in humans.*" *id* at 1567. [emphasis added]

Given the clear, direct, and on-point teachings of this case, the next question is whether the applicable law has changed since 1995. The *Brana* case has not been reversed. Indeed, the opinion in the *Brana* case is wholly consistent with the current Examining Guidelines, because both the opinion and the Guidelines cite *In re Marzocchi*, 439 F.2d 220, 223, 169 USP 367, 369 (CCPA 1971) for the same point:

> 2-Burden on the Examiner - MPEP 2164.04 and In re Brana 51 F2d.3d 1560, 1566:
>
> The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. If an examiner can provide reasons sufficient to create a reasonable doubt as to the accuracy of a particular broad statement put forward by applicant as enabling support for a claim, a rejection under 35 U.S.C. 112, first paragraph can be made. A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used

> in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. Citation omitted.

B. Application of the Applicable Law to the Current Application.

Under the cited law, both the case law and the Examination Guidelines, where a specification disclosure contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, the disclosure must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein. So, the burden is on the Examiner to show that there is some basis to disbelieve the disclosure with respect to the material described in sub-claims 37-39. Such a rejection can be overcome by pointing to experimental results, which may be *in vitro*, and may be supplied after the file date, provided the new data supports the existing disclosure. In this case, the base claim has admittedly been enabled, and the presently claimed material was disclosed in the application, claimed in the parent patent, and used in an Example in both the parent patent and the present application. This material is enabled by the text of the present application.

C. There is no basis to reject the teachings of this application.

1. The claimed invention is acknowledged to be enabled.

It is the claimed invention that must be examined. The claimed invention is:

A method of transfecting antigen presenting cells, the steps comprising

selecting a gene delivery complex that targets antigen presenting cells, comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives,

and applying the complex to the skin or mucosa surfaces of an animal,

wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter. This method is acknowledged to be enabled by the application. The question raised by the Examiner is whether the specification enables the dependent limitations, wherein the protein is from a human immunodeficiency virus (Claim 37); that is replication-defective (38); by virtue of being integration-defective (39).

The Examiner has taken the position that it is insufficient to show that the method induces an immune response (Applicants point out that their burden is to show that the method transfects antigen presenting cells); that something further, a "statistically significant" "therapeutic or prophylactic effect," that is, "CTL response...adequate to treat or prevent HIV" or "that the *virus* [emphasis added] does not replicate too much and cause disease." Stripped of all the excess verbiage, this is a requirement for either human clinical trials, or enablement of something the applicants have disclosed does not exist.

The USPTO examines an application to determine whether the claimed invention is supported by the text of the application. A single experiment is all that is necessary to establish patentability. Whether a "statistically significant" "therapeutic or prophylactic effect" is in fact present is a matter for the FDA, not the USPTO.

2. The raw materials in question are used in the Experiments

The applicants note that they have pointed out, *supra*, that a replication-defective, integration-defective set of proteins derived from HIV was used in this application to induce an immune response *ex vivo*, to demonstrate the utility of the raw materials being used, that the new method, which is an alternative to the *ex vivo* procedure used in Example 4, was proven up with a marker gene, and that the text of the application at Example 9 discloses that this invention demonstrates that *in vitro* isolation of DC is not required to transfer genes into Langerhans cells, or for gene expression in the lymphoid organs. The raw material described in Claims 37-39 was used in several experiments in the text of the text of this application, and transfected cells *in vitro* and using the *ex vivo* procedure. Use of the raw material is enabled.

3. The Declaration shows a therapeutic result

With respect to the allegations that no evidence that the CTL response is therapeutic or prophylactic in nature, it is noted that the Declaration of Dr. J. Lisziewicz dtd April 27, 2001, filed May 1, 2001 (Evidence Appendix – 3), was filed in the parent patent case and made of record in this case at least as of the date of filing February 21, 2002. This Declaration identifies one of the inventors, a prominent researcher in the field of the invention, discusses the correspondence between the animal model and the course of HIV infection in humans (Background paras 1-3) the similarity of response to drug therapy (para. 4), and the therapeutic benefit of virus-specific T cell mediated immune responses (para. 5). This Declaration further compares the best-available drug treatment (Efficacy, para 1), an enhanced, innovative drug treatment (Efficacy, para 2), the limits of the innovative drug treatment (para. 3) and the novel immune therapy involving the use of a complex of PEI-mannose and plasmid DNA encoding an integrase-defective SHIV in sugar-water solution (paras. 4 and 5). The animals' response to treatment is discussed in detail

(Efficacy, paras. 6-10), and summarized as showing increased CTL response associated with control of virus replication and improved survival time (Efficacy, paras. 11 and 12) The inventor states that the result, control of virus replication after the interruption of drug treatment during chronic infection or AIDS, is new. (Id.)

4. Peer-reviewed articles show a therapeutic result

Further, the cited publications by the inventors confirm the statements that are already in the application. For example, the application discloses that CTL responses are associated with therapeutic effects at page 4, lines 7-11: "Expression of foreign genes in antigen presenting cells (APC) may be used to generate efficient CTL response in animals. Therefore, gene transfer and genetic modification of APC has the potential to generate effective vaccine and therapeutic approaches ...." That is, the application discloses that generation of a CTL response is a legitimate marker for a therapeutic effect, and the peer-reviewed journal articles confirm that others agree with the inventors on this point.

See, for example, Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/Aids" J Invest Dermatol, 2004 detailing the use of the presently claimed invention to produce CTL responses; (Evidence Appendix – 4)

Lisziewicz, et al., "Control of Viral Rebound through therapeutic immunization with DermaVir", AIDS 2005, 19:35-43 which discloses studies showing low toxicity, enhanced viral control, and enhanced longevity; (Evidence Appendix – 5) and

Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Type 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells J Virol. Aug 2001, p. 7621-7628, (Evidence Appendix – 6) where the Examiner's technical questions about the differences between a replication-defective retroviral particle and plasmid DNA encoding the same are addressed. Expression of viral antigen by plasmid DNA is compared to that of the replication-defective control in primay human lymphocytes, macrophages, and dendritic cells in Fig. 1 b-d.

5. Where the Applicants have experimental results, the state of the art is irrelevant

The Examiner's comments about the state of the art at the time the application was filed are true to the extent that the field was unpredictable; however, it does not follow that this application must set forth whatever any prior art references predicted to be needed. This application sets forth the details of basic research into the physiological mechanisms of raising a CTL response, and discloses important and useful advances in new materials, a theoretical and practical basis for targeting antigen presenting cells, and a method of vaccination that does not require injection. It is not at all surprising that the disclosure of this application does not conform to that of the predictions in the prior art. The standard for

invention is that the subject matter is new, useful, and non-obvious. If the present invention were merely in the ambit of the prior art predictions, it would be properly rejected for being either not new, or obvious over the references currently cited.

The Examiner's comment that "it was also unknown how to make a retrovirus (changed in this rejection to "HIV vector") with the adequate amount of replication that would provide an adequate cellular immune response without causing disease" is disingenuous. The Examiner has continually refused to recognize the experimental evidence distinguishing between a "replication-defective retrovirus" and a "DNA encoding a replication-defective retrovirus." Mere substitution of a language change in this rejection does not make it valid. The present invention does not use a retrovirus with a finely-tuned reproductive capacity. In brief, a plasmid DNA encoding a replication defective, integrase-defective HIV is not the same thing as the corresponding viral particle, and the difference in the materials has been exploited by the inventors.

The Examiner's discussion of the experimental support offered by the Applicants does not consider the teachings of the application or the experiments as a whole. The *in vitro* data complements the *in vivo* data. The experimental support in the application must be taken as a whole, for what each experiment provides. The publications are cited to confirm the statements in the text of the application, and were never suggested to be separate, enabling disclosures.

The Examiner's criticism that the subsequent publications by the inventors contain experiments under a variety of conditions is inapt. For example , the Examiner makes much of the use of a tradename, DermaVir, in 2005 article that cited another article, Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Tye 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells" J Virol.(2001) pp 7621-7628. However, the referenced 2001 article discloses the construction of plasmid DNA encoding the replication-and integration-defective pLW/int- as the raw material in terms that clearly are acceptable to those of ordinary skill in the art. This is the material used in Example 1, page 18, line 31.

The Examiner's statement that the article by the inventors, Lori, et al., "Cellular Immunity and DNA vaccines for the treatment of HIV/AIDS Curr. Me. Chem. - Anti-Infective Agents, 3 (2004) pp 31-41 (Evidence Appendix 7), somehow renders the invention disclosed in this application unenabled because that article reports the failure of the first phase III HIV preventive vaccine trial (AIDSVAX B/B) is incorrect as a matter of law and as a matter of fact.

This kind of rejection has been considered, and found to be unacceptable. "We hold as we do because it is our firm conviction that one who has taught the public that a

compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans." *In re Brana* at 1567, quoting *in re Krimmel* 292 F2d 953, 130 USPQ at 219.

In addition, the failure of that vaccine trial merely confirms the inventors' own disclosure of the need for other materials. AIDSVAX B/B is a preventive vaccine designed to produce an antibody response (Evidence Appendix 7, col. 1, 2nd para.)

That trial demonstrates failure of others, and the result was predicted in another application by the present inventors, 08/803,404 (Evidence Appendix – 2), at page 3, first paragraph where vaccines directed to the production of an antibody response were disclosed to be problematic for HIV. The present inventors, in that application, proposed raising a different kind of immune response, using a different kind of material, that is, a method for raising a cellular immune response in a mammal, the steps comprising transducing antigen presenting cells selected from the group consisting of Langerhans cells, dendritic cells and mixtures thereof, with a plasmid DNA construct that encodes a replication-defective retrovirus, and exposing a mammalian host to the cells in a manner that allows the cells to express the construct in the lymphoid organs of the host, whereby a cellular immune response to the retrovirus is raised by the host. This is an alternative approach offered at a time when it was much needed, as confirmed by the Ready reference cited by the Examiner.

The Lori (2004) (Evidence Appendix – 7) article does discuss the present invention: "our DC targeted HIV vaccine, DermaVir, a topical, therapeutic vaccine that has demonstrated immunological and clinical benefits in rhesus macaques" at page 32, Column 1, 1st full para, lines 1-5 *up*. The article presents pre-clinical studies, page 38-39, a theoretical basis to explain why the vaccine differs from other vaccines (page 39, 2nd full para) and a suggestion for its treatment as a new antiretroviral approach complementary to that of various drug classes (page 39, paragraph bridging Cols 1 and 2). This is by no means an indication that the material has no therapeutic value.

D. Conclusion – This Enablement Rejection must be withdrawn

The Examiner's requirement to show an effect beyond that of the claimed invention is legal error. The Examiner's alternative requirement that, in order for the presently claimed invention to be enabled, the text of the specification must show anything other than how one of skill in the art can make and use the claimed invention, that is, to include any number of items that those in the prior art or analogous art may have predicted would be needed, is also legal error. The Applicants have properly stated the applicable law, which does indeed relate to the current rejection for alleged lack of enablement.

The Applicants recognize the difference between the Examiner and the USPTO, and think that responsibility for attempts to evade the settled law of the Federal Circuit rests with the USPTO, not the Examiner. Further, the applicants have a right to a clear and candid statement of the examination policy of the USPTO, which should be applicable to all art groups. If the USPTO has a policy try yet again to push for a ruling that clinical results will be required for medical inventions, or that prior art references can be used to determine the content of an application's disclosure, or that subsequent publications can "unenable" the disclosure in a patent application, then the applicants have a right to know this and have the policy opened up to public debate. The Applicants have reviewed the status of the applicable law relating to any requirement for data showing a "therapeutic or prophylactic effect" or in the alternative, a laundry list of requirements pulled from prior art documents, or any use of subsequent publications to "unenable" a disclosure, and cannot find them in the case law, MPEP, or Examiner's training materials.

The Applicants point out that they have, as a result of some sort of acknowledged but undefined policy of the USPTO, have been subjected to extraordinary expense, delay in prosecution, and loss of term for their patent applications, based on the field of interest rather than the merits of the case. Accordingly, an extension of patent term equal to the entire span of prosecution of this application is requested.

3. Indefiniteness

Claims 23-26, 28, 30-33, 35 and 37-43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 23 remains indefinite because the body of the claim merely requires selecting a gene delivery complex that targets APCs and applying a complex to the skin or mucosa surface of an animal, while the preamble requires transfecting of APCs. The body of the claim never requires transfecting APCs or expressing the immunogenic protein in APCs. The preamble and the body of the claim do not have a nexus, thereby making the claim as a whole unclear. The should claim requires a clear positive step in the body of the claim indicating APCs are transfected to be commensurate in scope with the preamble of the claim. Otherwise, those of skill would not be able to determine whether transfecting APCs was an intended use (optional) or whether transfecting must occur.

Applicants' argue the claims were amended to conform to language "favored by the examiner" (pg 24 of response). Applicants' argument is unfounded. The language of the claims remains unclear. Applicants' have not provided any substantive arguments for any of the indefiniteness rejections.

Claim 23 remains indefinite because it is unclear if "transfecting" is limited to transfection with plasmid or if the term encompasses infection with a viral particle. The specification does not define "transfection". *Note: see Summary of Claimed Subject Matter, 1st para.* Applicants argue the term was inserted "to comply with what they

thought was a demand by the examiner." Applicants do not provide any suggestions or any other arguments. Applicants' arguments are not substantive. The examiner merely rejected the previous term "transducing" under 112/2 nd in the office action of 3-10-04.

Claim 23 remains indefinite because the metes and bounds of what applicants consider "applying" to the skin cannot be determined. It is unclear if the phrase is limited to putting the complex on the skin or if the phrase encompasses subcutaneous injection which results in delivery of the complex under the skin. It is unclear if intravenous injection is encompassed by the phrase because such an injection does require contact of the complex to the skin when the injection passes through the skin. Applicants previously argued the phrase had support on pg " 16, line 34, where application to the skin is distinguished from injection." Applicants' argument was not persuasive. Pg 16, line 34, merely states, "The complex can be applied to the skin or mucosa surfaces directly." The citation does not discuss injection or distinguish "applying" -from "injecting." Applicants' arguments do not provide any new arguments or address how to interpret the phrase. As such, one of skill would not be able to determine when they were infringing on the claim.

Claim 23 is indefinite because the phrase "gene delivery complex that targets antigen presenting cells" is unclear. It is unclear if the phrase encompasses any gene delivery complex that transfects APCs or if the gene delivery complex has a particular structure or preference for APCs. If the gene delivery complex has a particular structure or preference for APCs, the metes and bounds of those gene delivery complexes that have a preference for transfecting APCs cannot be envisioned.

Claim 30 remains indefinite because the phrase "method of claim 28, wherein the complex comprises a 5:1 ratio of polyethylenimine derivative nitrogen per DNA phosphate" remains unclear. Claim 30 does not limit the complex to having polyethylenimine or polyethyleni mine derivative; therefore, limiting the complex to having a 5:1 ratio of PEI nitrogen per DNA phosphate without first limiting the complex to one having PEI does not make sense because the complex can made with sugar (see claim 23). Furthermore, claim 30 refers to a 5:1 ratio of polyethylenimine derivative. It is unclear if applicants are attempting to limit the ratio or the compound used for gene delivery. Overall, the phrase is unclear. Applicants' have not provided any new arguments to this rejection.

Claim 31 remains indefinite because it is unclear whether the phrase "is formulated in a glucose solution" is limited to adding PEI, PEI-glu, PEI-gal, or PEI-man to a solution of glucose + water or if the phrase encompasses PEI-glu, PEI-gal, or PEIman + water. The specification teaches PEI may be glycosylated (pg 21, Table 1) or solubilized in glucose (pg 22, line 35). Overall, it is unclear whether the phrase is limited to PEI or PEI derivative added to glucose + water or if the phrase encompasses adding PEI-glu to water. Applicants' previous arguments relating to "unexpected results" were not persuasive because they did not address the indefiniteness of the phrase. Applicants argued both scenarios described by the examiner are encompassed by the phrase; however, PEI-glu added to water cannot be "a glucose solution" because the glucose will not solubilize in the water. Applicants'have not provided any new arguments to this rejection.

Response – Indefiniteness

The Applicants have a right to uniform application of the patentability standard (MPEP 706). Piecemeal Examination is to be avoided (MPEP 707.07(g)). Certain technical objections, (e.g., negative limitations, indefiniteness) should not be made where the examiner, recognizing the limitations of the English language, is not aware of an improved

mode of definition. (MPEP 707.07(g)). Inventions relating to HIV/AIDS and cancer are specifically important, and suitable for expedited processing. (MPEP 708.02 X.) And, applications that are substantially allowable should be considered special and prompt action taken to require correction of formal matters (MPEP 1301). Even in ordinary cases, the Examiner should never overlook the importance of his or her role in allowing claims which properly define the invention (MPEP 706). The examiner's action should be constructive in nature and when possible should offer a definite suggestion for correction (MPEP 706 II).

The Applicants submitted a set of Claims that could have been allowed on the first office action in this case. The Applicants have, in good faith, used the text of the parent application's claims, and consulted with the Examiner to draft the present claims. Despite their own clear right to act as their own lexicographers, the Applicants have abandoned their original language in an effort to conform the claims to their invention to that favored by the Examiner, and repeatedly amended the claims for that purpose. The Applicants have pointed to support in the application and also asked, in writing, for a definite suggestion, as is their right under MPEP 706, and the Examiner has not responded. It is noted that the Examiner has failed to proffer acceptable language and failed to recognize the distinction between an "argument" and a statement regarding the scope of the claims that will necessarily give rise to an estoppel, should the patent ever be subject to challenge. It is noted that the Applicants have in the past attempted to amend Claims in response to the present Examiner's criticisms, to no good result.

Accordingly, the Applicants respectfully request that, pursuant to MPEP 707(g), the present rejections be withdrawn because the Examiner has impliedly admitted that he is not aware of an improved mode of definition.

Claim Rejections - 35 USC § 102

4. Anticipation

Claims 23-26, 28, 30-32, 35, 37, 40 41 and 43 remain rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Carson (US Patent 5,679,647) for reasons of record.

Parent application 60/058,933 did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Therefore, claim 23 does not get priority back to parent application 60/058,933 (filed 9-15-97). Parent application 09/153,198 (filed 9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9. Therefore, claim 23 has priority to 9-15-98.

The Behr reference is said to have taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to

a promoter suspended in 5% glucose Note: the stock solution was 5%, diluted twice (col. 12, lines 53-57). Luciferase is alleged, without citation to any evidence whatsoever, to be an immunogenic protein because it is foreign to mammals and said to induce an immune response in mammals. Behr is said to have taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr is said to have taught the DNA could encode an HIV peptide (col. 3, lines 57-67). The Examiner points to no teaching, but argues that the method of Behr inherently results in transfecting APCs because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell", item 3). While explicitly not relied upon for the basis of the rejection, Carson is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin that transfects dendritic cells (col. 36-37, Examples 11-12). It is noted, however, the phrase "transfecting antigen presenting cells" in the preamble has not been deemed to have patentable weight in considering the art because the body of the claim does not require transfecting APCs. [sic.]

Claims 25, 26 and 43 are said to be included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 are said to encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are said to be included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are said to be included because administering the complex to the skin/mucosa as taught by Behr inherently would act activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

The Examiner remarks that Applicants argue the Examiner has erred legally because Behr does not teach all the limitations of the claims (pg 26, first full paragraph, of arguments). Applicants' argument is not persuasive because applicants do not point to one specific limitation that Behr fails to teach. [sic] All the limitations in the claims have been addressed in the rejection.

The Examiner remarks that the Applicants argue the Examiner has erred factually because he uses speculation and not fact to support the assertion that the luciferase protein made by an insect is inherently immunogenic as claimed (pg 26, first full paragraph, of arguments and pg 30 of arguments). The Examiner takes the position that the applicants' argument is not persuasive because, he asserts, the examiner has provided scientific reasoning that the luciferase protein would be immunogenic: because it is foreign to the animal to which the gene delivery complex is applied. Furthermore, the claims do not require inducing an immune response. [sic] Finally, Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) is said to have taught that luciferase induces antibodies in rats (second to last sentence of the abstract). The Examiner contends that luciferase must be immunogenic as claimed in any animal other than fireflies because it is a protein isolated from fireflies and because proteins isolated from one animal and introduced into another animal are recognized as foreign by the immune system and cause an immune response (Kuby, ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9). Applicants' point to the description of luciferase by bd biosciences, which states the luciferase is non-toxic. Applicants' argument is said to be not persuasive. Toxic is defined as the quality of being poisonous, especially the degree of virulence of a

toxic microbe or a poison (On-line medical dictionary definition of "toxicity"). However, the claim merely requires the protein is "immunogenic!' which is defined as capable of inducing an immune response (Online Medical dictionary definition of "immunogenic"). Thus, luciferase is non-toxic but still meets the definition of an "immunogenic protein" as claimed because it induces an antibody response in animals other than fireflies.

Applicants argue Behr does not teach targeting APCs. Applicants' argument is said to be not persuasive. The Examiner remarks that the claims encompass any method that results in transfecting APCs (see 112/2nd), and states that Carson provides evidence that the method of Behr inherently results in transfecting APCs.

Applicants argue intracerebral injection of naked DNA encoding luciferase failed to work as discussed by Behr in Example 14 (column 13, lines 9-10; pg 28 of arguments). Applicants' argument is not persuasive. The claims relate to using DNA in combination with sugars, PEI or PEI derivatives. While DNA was not successfully transferred to the brain using naked DNA, Behr successfully transferred DNA to the brain in the presence of glucose and PEI (col. 13, lines 6-10; Fig. 12). Furthermore, the claims relate to applying the gene delivery complex to the skin or mucosa, not the brain as discussed in Example 14 of Behr. [sic]

Applicants' argue the method of Carson would suffer from "low efficiency, in transfecting APCs. Applicants' argument is not persuasive. Any "efficiency" is adequate to provide evidence that the method of Behr would transfect APCs, even if it were "low." The claims do not require a particular transfection efficiency. In fact, the body of the claim does not even require transfecting APCs.

Applicants argue the advantage of the claimed invention is that is can merely be applied to the skin (pg 29 of arguments). Applicants' argument is not persuasive. Behr taught topical, cutaneous, oral, rectal, vaginal, parenteral and intranasal application (col. 6, lines 1-4), which is equivalent to applying the gene delivery complex to the skin or mucosa as claimed. The claims are not limited to topical administration of the gene delivery complex.

Applicants argue they used GFP in their experiments. Applicants' argument is not persuasive. The claims do not require the DNA encodes GFP. Applicants' arguments regarding the transgenic bunny born to express GFP are moot because the GFP is recognized as a "self' protein in the transgenic bunny-, its immune system developed recognizing GFP as part of itself.

Applicants argue Carson does not provide a reasonable expectation of success because Carson used intradermal injection or a tine devise. Applicants' arguments are not persuasive. Arguments regarding an expectation of success in misplaced under 102. The teachings of Carson relate to applying the gene delivery complex to the skin using an intradermal injection or a tine devise. The claims do not exclude applying the gene delivery complex to the skin using an intradermal injection or a tine devise. The claims are not limited to applying the gene delivery complex to the skin topically.

Response – Anticipation

The Applicants have a right to uniform application of the patentability standard (MPEP 706). Piecemeal Examination is to be avoided (MPEP 707.07(g)). Inventions relating to HIV/AIDS and cancer are specifically important, and suitable for expedited

processing. (MPEP 708.02 X.) And, applications that are substantially allowable should be considered special and prompt action taken to require correction of formal matters (MPEP 1301). Even in ordinary cases, the Examiner should never overlook the importance of his or her role in allowing claims which properly define the invention (MPEP 706). The examiner's action should be constructive in nature and when possible should offer a definite suggestion for correction (MPEP 706).

The Applicants have requested a written statement by the USPTO stating the legal basis for failing to withdraw a 35 USC §102 rejection where the limitations are not found within a single reference, and for maintaining an inherency argument where no evidence exists that the supposed results (immune response to luciferase) have been obtained. No such response has been forthcoming.

A. Applicable Law – 35 USC 102

The Applicants note that the latest set of Examiner's Guidelines was modified in with respect to 102(e)(2), not relevant here, in 2000.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The **identical** invention must be **shown in as complete detail as is contained in the ... claim**. (emphasis added) The elements must be arranged as required by the claim. MPEP 2131. Multiple references may be used to (a) prove that a reference was an enabling disclosure, (b) explain the meaning of a term, or (c) show that a characteristic not disclosed in the reference is inherent (MPEP 2131.01). The burden is on the Examiner to first show that the claimed composition or machine is disclosed **identically** (emphasis added) by the reference, if an additional reference is to be used to show enablement (MPEP 2131.01 I.).

The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. (MPEP 2112.02)

The Behr Reference (Evidence Appendix – 12)

The Behr reference relates to the use of PEI as an adjuvant for gene therapy, preferably in conjunction with plasmid DNA, although a wide variety of other materials are disclosed as well. Gene therapy is disclosed to consist in correcting a deficiency or an abnormality (mutation, aberrant expression, and the like) or in effecting the expression of a protein of therapeutic value by introducing genetic information into the affected cell or organ (Col. 1, lines 11-15). Gene therapy is a field distinct from immunotherapy, and this reference discloses that immunogenicity, that is, the result obtained by the inventors, is to be avoided in this context (Col. 1, line 51).

The reference states that PEI can be used in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), in a wide variety of configurations, including using a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57; sugars are listed as useful for targeting the asialoglycoprotein receptors at Col 5, lines 64-65), for a wide variety of purposes (for example, the production of therapeutic products including enzymes, blood derivatives, hormones, lymphokines,...growth factors, neurotransmitters...synthetic enzymes, etc,, -- a list that includes thousands of items. See Col. 3, lines 29-44. Antigenic peptides are also listed at Col. 3, line 57-67, as well as antisense genes (Col. 3, line 45), sequences (Col. 4, line 1, and upstream signals to control therapeutic genes (Col. 4, lines 25-29) and that it can be used in formulations with a view to topic, cutaneous, oral, rectal, vaginal, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like (Col. 6, lines 1-4) in formulations that that might be isotonic sterile solutions, dry, water or saline (Col. 6, lines 9-12 as appropriate *to enable injectable solutions to be formed* (line 13, emphasis added). Both direct injection and topical administration are said to be preferred (Col. 6, lines 5-9), but only direct injection is shown in any experiments, and there is no disclosure of how to accomplish gene delivery by means of topical administration.

Claim Limitations Missing from the Behr reference

Among the differences between this reference and the presently claimed invention are that the reference does not disclose the transfection of antigen presenting cells, or the targeting of antigen presenting cells, a most significant subset of cells, and prominent by its omission, or formulations that can be used for needleless, *in vivo* delivery of genes into any cells, much less antigen presenting cells, or any *in vivo* method of delivery except injection.

Similarly, the reference does not disclose that glucose and PEI derivatives could be used in the claimed method (Claim 24) or that the PEI derivatives can target the mannose receptor instead of the asialoglycoprotein receptors (Claim 25), or anything about mannosylated polyethylenimine (Claim 26) or the manipulation of electrostatically neutral complexes to target antigen presenting cells (Claim 28) or the specific ratio of PEI to DNA that is preferred for different derivatives (Claims 30 and 42), that the glucose solution should be preferred for targeting antigen presenting cells (Claim 31), or that the range of glucose concentration in a method targeting antigen presenting cells is higher than that disclosed for general use for transfecting neurons in the Behr reference (Claims 32 and 33), or that a further step of receptor stimulation, tissue injury or cell injury might activate antigen presenting cells and therefore enhance a (disclosed in the Behr reference to be an undesired) immune response (Claim 35), or that proteins from human immunodeficiency

viruses can be used in the claimed method to transfect antigen presenting cells (Claim 37), or that the claimed method would be successful using a nucleic acid sequence encoding an integration-defective or replication-defective human immunodeficiency virus (Claims 38 and 39), or that a plasmid DNA can be successfully used in the claimed method (Claim 40), or that Langerhans cells can be targeted using the claimed method and materials (Claim 41), or that use of a sugar-modified polyethylenimine would be desirable (Claim 43).

The Carson Reference (Evidence Appendix – 13)

Carson is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin that transfects dendritic cells (col. 36-37, Examples 11-12). This is not true. The definition of the complex is apparently plasmid DNA only, and is referred to repeatedly as "naked" (e.g., Col. 30, line 41). These materials were formulated in saline solution (Col. 31, line 18). Both of the cited experiments rely on injection devices: intradermal injection of plasmid (Example X, column 35, line48) or a tyne device (Col. 37, line 16). The material from the Carson reference was tested in the Behr method, and did not work. Naked DNA formulated in a glucose solution was tested for transfection into brain tissue in the Behr reference (Example 14, Col. 13, lines 9-10), and found not to work in that experiment. Similar results were obtained in an *in vitro* experiment using saline solution and cultured neurons in the Behr reference (Example 13). Also, the Carson reference reports both CTL responses and antibody responses, which it attributes possibly to the location of injection, and which indicate uptake by different classes of cells. There is no discussion whatever about how to target APCs, as opposed to other types of cells, specifically.

Furthermore, this 1994 reference can be placed in perspective by the discussion in the present specification at page 6, line 8 et seq., of Arthur, et al "A Comparison of gene transfer methods in human dendritic cells," Cancer Gene Therapy, v. 4, No. 1, 1997 pp 17-25[2], which reports that the then-known *in vitro* methods of gene transfer suffered from low efficiency. That article reported that, of a variety of gene transfer methods were tried for human DC, only adenoviral vectors were a promising vehicle for genetically engineering human DCs (Abstract). The application also discloses at page 6, line 14-19 that, as of 1998, "known *in vivo* methods include ... intradermal subcutaneous and intramuscular injection of DNA. None of these methods have been shown to effectively deliver genes into antigen presenting cells, such as dendritic cells, much less delivery of genes through the skin into the Langerhans cells."

[2] This reference has been of record in the present case, as acknowledged by the Examiner on 8/9/01. A copy of the reference is enclosed at Evidence Appendix 10.

The present Invention

The present application is a division of United States Patent No. 6,420,176, which was drawn to a novel DNA complex for gene delivery. The present application relates to a method of transfecting antigen presenting cells, the steps comprising

selecting a gene delivery complex that targets antigen presenting cells comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives,

and applying the complex to the skin or mucosa surfaces of an animal,

wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter.

An advantage enjoyed by this invention is that the gene delivery complex need not be injected, but merely applied to the skin, according to the claimed method. The inventors have found, and the text of the application contains, experiments that demonstrate that both the wholly novel complex (DNA plus mannosylated PEI) and several other arguably non-novel complexes (DNA plus modified PEI, PEI with sugars, PEI alone, and sugars alone) also work in an elegant method for stimulating the immune system that does not rely on injection, added irritants or toxins, use of cultured cells or expensive new equipment such as a gene gun. The present application also discloses how to modify the teachings of the Behr reference so that the claimed antigen presenting cells can be targeted via the mannose receptor as opposed to the asialoglycoprotein receptor (at least at page 14, line 37 – page 15, line 15, and Example 6). These cells are disclosed to be capable of producing a CTL response (page 11, line 21) and proven to do so *in vitro* (Example 3), and *in vivo* (Example 4), and additional data submitted by the inventors shows that the immune response induced in this manner does not include antibody (humoral) responses using either the (injected) *ex vivo* or (applied to the skin) *in vivo* procedures. Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Type 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells"[3] J Virol, Aug 2001, p.7621- 7621-7628, at Abstract and p 7626, lines 12-15, 1st full paragraph. See also Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/AIDS J Inv Dermatology, 2004,[4] p. 6, col. 1, first paragraph, last 4 lines.

[3] Evidence Appendix 6
[4] Evidence Appendix 4

Analysis

To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference [emphasis added], and that it would be so recognized by persons of ordinary skill." "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." (citations omitted) *In re Roberts*, 169 F.3d 743, 49 USPQ2d 1949 (1999). "We do not see how a disclosure or combination of disclosures leaving one to rely on fortune in choosing the referred to material can function as anticipation. Absent a showing of some reasonable certainty of inherency, the rejection under 35 USC 102 must fall." *In re Brink*, 419 F.2d 914, 918, 164 USPQ 247 (1970).

B. Examiner's Arguments

The Examiner has not pointed to any disclosure or discussion within the Behr reference relating to the claimed method, nor of any disclosure that would guide one of ordinary skill in the art to choose from the many options available, to make the claimed invention or obtain its advantages. The Examiner has relied, however, on two arguments in an effort to make the rejection.

1. Inherency – Luciferase as an Immunogen

The Examiner points to Example 14 of the Behr patent, where a plasmid encoding a marker gene for luciferase was diluted in 5% glucose solution to about 3% glucose, and then diluted with PEI and injected into the brains of newborn mice, whose brains were subsequently an assayed for light emission as a sign of transfection into neurons. The reference comments that this experiment shows the advantages of the compositions of that experiment for gene therapy, that the plasmid with PEI was transferred efficiently into the brain of mice, and that no significant luciferase activity was observed when the plasmid alone was used.

There is no disclosure or discussion of antigen presenting cells, no disclosure or discussion of how to specifically target antigen presenting cells as opposed to neurons, no experiment reporting an immune response, yet the Examiner argues without citation that Luciferase is inherently an immunogen, and that because the Behr reference taught elsewhere and without more, "topical application," that the Behr reference inherently teaches that the material in Example 14, *if placed on the skin* would target *antigen presenting cells*, because antigen presenting cells are in the skin. At best, this is an argument that it might have been obvious to try an experiment, and does not rise to the clear disclosure required to anticipate the claims.

The present application at page 6, lines 4-11 cites to a fairly contemporaneous reference (Arthur, et al.,) that indicates that different types of cell lines have different responses to transfection techniques and that of the methods screened, only adenoviral vectors showed promise for genetically engineering human DCs. (Abstract), and the application states that that the known techniques and materials had not been shown to effectively deliver genes into antigen presenting cells, such as dendritic cells, much less delivery of genes through the skin into the Langerhans cells. There is no reason to discredit this disclosure, especially in view of the Examiner's vigorous urging that the art at the time was unpredictable. Thus it is not clear that the unaltered material disclosed in Experiment 14 would inherently transfect antigen presenting cells.

It is not at all clear that luciferase will inherently cause an immune response. Luciferase is a commercially available reagent from, among many others, BD Biosciences, who characterize the material as follows on their web site[5]:

http://www.bdbiosciences.com/pharmingen/products/display_product.php?keyID=76

Luciferase Reporter Assay Applied Reagents

> Since the firefly beetle (Photinus pyralis) luciferase gene was introduced to molecular biology, it has provided a method of utilizing biological light production as a tool for research. Luciferase interacts with its cognate substrate luciferin to produce light emission peaking at 562 nm. For use in the laboratory, this form of luminescence can yield a very sensitive non-radioactive assay. Firefly luciferase can be reliably expressed from various expression vectors and in a diversity of organisms as a reporter in studies of gene regulation. Luciferase reporter assay systems are currently one of the best **non-toxic**, rapid and sensitive methods to measure gene expression. The assay is based on the detection of luciferase activity which correlates with transcription due to DNA regulatory elements in genes, mutations within those elements as well as responses to extracellular and intracellular signals. (emphasis added)

CTL responses are cellular immune responses. For the purposes of gene therapy they are considered toxic because they result in the elimination of the cells expressing the DNA, which are considered to be the "cured" or "therapeutic" cells. (At minimum, elimination of the cured cells would result in elimination of the therapeutic and prophylactic benefit). That is why the Behr reference taught that immunogenicity is to be avoided in this context (Col. 1, line 51). If marker genes were used that resulted in a CTL response *in vivo*, the transfected cells might be destroyed fairly quickly, and the experiment might appear to fail. Thus a desirable marker gene is one that is likely to provoke little, if any, immune response, to avoid interfering with the tests.

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[5] Evidence Appendix 8B

It is noted that the Applicants have used a different marker gene in their experiments, a green fluorescent protein gene derived, it is believed, from jellyfish. Such a gene was used to produce a "GFP bunny," that is, a rabbit that glows in the dark, if stimulated by the proper light source[6]. http://www.ekac.org/gfpbunny.html#gfpbunnyanchor The Examiner's statement to the contrary, if this marker gene inherently stimulated an immune response, assuming the animal could have been produced at all, the rabbit would have died from an autoimmune reaction shortly after it began to produce the protein. This existence of this genetically altered animal indicates that not all marker genes are inherently cause immune responses, and so one of ordinary skill in the art would not read the experiment to show that the material disclosed in Example 14 would inherently cause an immune response. The Examiner's assumption, that all proteins inherently cause immune (toxic) responses, has been fairly met because the applicants have pointed out that not all proteins cause such responses, and the genes that encode some of them have been found and used for marker genes.

2. *Expectation of Success*

Carson is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin that transfects dendritic cells (col. 36-37, Examples 11-12). Both of these experiments rely on devices: intradermal injection of plasmid in saline solution (Example X, column 35, line48) or a tyne device (Col. 37, line 16). The "complex" as discussed above, is "naked" DNA, which was tested in the Behr reference and found ineffective. This reference adds nothing to the Behr reference.

Furthermore, this 1994 reference can be placed in perspective by the discussion in the application at page 6, first full paragraph, of Arthur, et al "A Comparison of gene transfer methods in human dendritic cells Cancer Gene Therapy, v. 4, No. 1, 1997 pp 17-25, which states that that indicates that different types of cell lines have different responses to transfection techniques reports that the then-known *in vitro* methods of gene transfer suffered from low efficiency. The application also discloses at page 6, line 14-19 that, as of 1998, "known *in vivo* methods include ... intradermal subcutaneous and intramuscular injection of DNA. None of these methods have been shown to effectively deliver genes into antigen presenting cells, such as dendritic cells, much less delivery of genes through the skin into the Langerhans cells." See also Pollard, et al., "Polyethylenimine but not cationic lipids promotes transgene delivery to the nucleus of mammalian cells" J. Biol. Chem. Vol. 273, No. 13, pp. 7507-7511 (1998) discussed at page 15, lines 3-6 of the application. [7] One

[6] Evidence Appendix 9
[7] Evidence Appendix 11

of the conclusions drawn by the authors of that 1998 article was that barriers to gene transfer vary with cell type (Abstract, and p. 7510, col. 2, last full para, lines 1-8 UP). This disclosure is especially credible in light of the Examiner's vigorous insistence, in another context, that the art was at the time unpredictable. The Carson reference, which related to intradermal and intramuscular injection of DNA had not been shown to be effective as of several years later. It does not yield any indicator that the Behr reference could be successfully altered in the manner disclosed in the present application, and so cannot be relied upon to support an inherency argument.

C. Conclusion

The Behr reference does not disclose the claimed method because it does not indicate how to pick and choose among its teachings to transfect a different class of cells, dendritic cells, via a different receptor, the mannose receptor, directed to what is for the Behr reference, a toxic response. Example 14 of the Behr reference does not include a material that one of ordinary skill in the art at the time the invention was made would interpret to inherently cause an immune response. The gene is a marker gene, and marker genes are selected for their low toxicity, one aspect of which is lack of tendency to produce immune responses. The Carson reference cannot reasonably be said to yield a reasonable expectation of success, much less the degree of certainty needed to maintain an inherency rejection, to an experiment reconstructed by hindsight from the Behr reference. That is because subsequent peer-reviewed publications by others, the Behr reference itself, and the text in the present application all disclose that the techniques used in the Carson reference had not been shown to yield effective transfection in antigen presenting cells as of the file date of the present application.

35 USC § 103

5. Obviousness

Claims 23-26, 28, 30-32, 35, 37-41 and 43 have been newly rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Carson (US Patent 5,679,647) and in view of Holler (US Patent 5,908,923).

Parent application 60/058,933 (9-15-97) did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Parent application 09/153,198 (9-15-98) described complexing DNA with PEImannose in a 5-10% glucose solution on pg 26, lines 1-9; therefore, claim 23 has priority to 09/153,198 (9-15-98).

Behr is said to have taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (Note: 3% or so. A 5% stock solution was diluted with two

other solutions in a two-step process, therefore the end result is clearly not a 5% concentration of glucose.) (col. 12, lines 53-57). Luciferase is said to be an immunogenic protein because it is foreign to mammals and is alleged without citation to induce an immune response in mammals. Behr is said to have taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr is said to have taught the DNA could encode a peptide from HIV (col. 3, lines 57-67). The Examiner concludes that the method of Behr inherently results in transfecting APCs because dendritic cells. (*sic.* The sentence is taken to continue in the matter of the rejection above, "(a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell,"item 3)." Carson is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin transfects dendritic cells (col. 36-37, Examples 11-12). The Examiner notes that case law established that reliance upon inherency in an obviousness rejection (103) instead of an anticipation rejection (102) is proper. *In re Skoner, et al.*, 186 USPQ 80 (CCPA). It is noted by the Examiner, however, that the phrase "transfecting antigen presenting cells" in the preamble is not not being considered to bear patentable weight in considering the art because it may not occur. [sic]

Claims 25, 26 and 43 are said to be included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are said to be included because Behr is said to have taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral, (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are said to be included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

The Examiner admits that the Behr reference did not teach using a plasmid encoding a protein from a replication-defective, integrase-defective HIV. However, the Holler reference is said to have taught a plasmid encoding a replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54).

Thus, the Examiner states that it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a gene delivery complex comprising a plasmid encoding an HIV protein to the skin/mucosa of an animal as described by Behr, wherein the plasmid encoded a replication-defective, integrase-defective HIV as taught by Holler. The Examiner states that one of ordinary skill in the art would have been motivated to make the HIV replication.

The examiner acknowledges that interpreting the claims as not requiring treating or preventing HIV under 103 is different from interpreting the claims as requiring treating or preventing H IV under the written description and enablement requirements; however, both interpretations are said to be reasonable and all rejections are said to have been fully supported. The Examiner remarks that, assuming arguendo that the limitation of treating or preventing HIV cannot be read into the claim, the burden required to show motivation to combine Behr and Holler for obviousness purposes is not high because the claims merely require applying a vector encoding HIV to the skin or mucosa of an animal, because Holler (and numerous other references) taught a vector encoding HIV proteins for use in vivo and

because Behr suggested using a vector encoding HIV proteins in his method of transfecting in vivo.

Applicants' specific arguments about Behr and Carson have been addressed above under 102.

Applicants' arguments regarding "efficiency" have been addressed above under 102.

Applicants mention clinical trials (pg 42, "A vaccine according... ") but do not correlate any clinical trial to the teachings in the specification or the claims.

Applicants argue the claims require targeting APCs. Applicants' argument is not persuasive. The method of applying a gene delivery complex to the skin or mucosa allegedly taught by Behr is said to transfect APCs, which is equivalent to "targeting APCs" as claimed. Furthermore, the Examiner remarks that the Behr reference used DNA combined PEI which applicants clearly state is part of their invention.

Applicants argue the examiner has merely pieced together the references to come up with motivation to experiment. Applicants' argument is not persuasive. The examiner has provided a reference teaching a specific plasmid encoding a replication-defective, integrase-defective HIV (Holler) for use in the method of Behr and motivation for why one of ordinary skill would want to combine the references. "Motivation to experiment" is a mischaracterization of the motivational statements provided by the examiner; the motivational statement provided by the examiner is based on the desire to prevent HIV infection or death of the animal receiving or applying the gene delivery complex. Holler provides evidence for the desire to use a replication-defective, integrase-defective HIV to induce an immune response in an animal without causing infection or death. It is noted that the claims do not require inducing an immune response against HIV or treating or preventing HIV; therefore, the burden required to combine the references for prior art purposes does not bear the onus of treating or preventing HIV.

Applicants argue Holler merely teaches that the replication-defective, integrasedefective HIV is usable in vivo but did not expressly use the HIV in vivo. Applicants' argument is not persuasive. Neither Behr nor Holler needs to provide examples of using the virus in vivo. Behr is being relied upon for the step of applying a plasmid encoding an HIV protein to the skin of an animal.

The combined teachings of Behr and Holler said to provide a reasonable expectation of successfully transfecting cells because Holler transfected CEM (a lymphoblastoid cell line) with integrase-defective HIV. Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of successfully transfecting APCs by applying the plasmid encoding the HIV taught by Holler to the skin or mucosa as taught by Behr.

5. Response – Obviousness

A. Applicable Law

Whether patents are allowable in a given particular field of art is not a question of Patent and Trademark Office discretion but of law, and examiners have no discretion to deny patents to inventions meeting the statutory criteria. *Animal Legal Defense Fund v. Quigg*, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985).

Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. The four factual inquires enunciated therein as a background for determining obviousness are as follows:

(A)Determining the scope and contents of the prior art;

(B)Ascertaining the differences between the prior art and the claims in issue;

(C)Resolving the level of ordinary skill in the pertinent art; and

(D)Evaluating evidence of secondary considerations. (MPEP 2141)

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art combination must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the expectation of success must be both found in the prior art, not in the applicant's disclosure. MPEP 2143. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) (MPEP 2143.01 I).

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1071, 5 USPQQ2d 1596 (Fed. Cir. 1988).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (MPEP 2143.01 III).

If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) If the proposed modifications or combination of the prior art would changed the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); see also MPEP 2143.01 V.

B. Factual Background: The Claimed Invention, the Scope and Content of the Prior Art, the Differences between the Claimed Invention and the Prior Art

The Behr Reference (Evidence Exhibit – 12)

The Behr reference relates to the use of PEI as an adjuvant for gene therapy (Abstract), preferably in conjunction with plasmid DNA, although a wide variety of other materials are disclosed as well. Gene therapy is disclosed to consist in correcting a deficiency or an abnormality (mutation, aberrant expression, and the like) or in effecting the expression of a protein of therapeutic value by introducing genetic information into the affected cell or organ (Col. 1, lines 11-15). Gene therapy is a field distinct from the subject matter of the present invention, which is immunotherapy, and the reference discloses that immunogenicity is to be avoided in this context (Col. 1, line 51). Thus the entire discussion of whether the GFP marker gene used in the Behr reference could be construed as an immunogenic protein is inapt. First, no such reaction was shown. Second, such a reaction would have rendered the experiments a failure due to toxicity. If the cells inherently provoke an immune response in vivo, they get killed off very rapidly, and do not produce measurable amounts of the marker protein.

The reference states that PEI can be used in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), in a wide variety of configurations, including a wide range of amine to phosphate mol ratios (0.5 – 50 at Col. 2, line 50) without any distinction as to what might be accomplished by varying such ratios, using a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57; sugars are listed as useful for targeting the asialoglycoprotein receptors at Col 5, lines 64-65), for a wide variety of purposes (for example, the production of therapeutic products including enzymes, blood derivatives, hormones, lymphokines,...growth factors, neurotransmitters...synthetic enzymes, etc,, -- a list that includes thousands of items. See Col. 3, lines 29-44. Antigenic peptides are also listed at Col. 3, line 57-67, as well as antisense genes (Col. 3, line 45), sequences (Col. 4, line 1, and upstream signals to control

therapeutic genes (Col. 4, lines 25-29) and that it can be used in formulations with a view to topic, cutaneous, oral, rectal, vaginal, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like (Col. 6, lines 1-4) in formulations that that might be isotonic sterile solutions, dry, water or saline (Col. 6, lines 9-12 as appropriate *to enable injectable solutions to be formed* (line 13, emphasis added). Both saline (Example 13 and glucose Example 14) formulations are disclosed, without any distinction as to any advantage that might be obtained. Both direct injection and topical administration are said to be preferred (Col. 6, lines 5-9), but only direct injection into the brain for the transfection of neural tissue is shown in any experiments, and there is no disclosure of how to accomplish gene delivery by means of topical administration, or any disclosure whatever of the transfection of antigen presenting cells, or the provocation of any type of an immune response.

This reference has disclosure consistent with that for a new material or a new use for a material with potentially wide application in a given field. What is beyond the scope of this reference is specific instruction as to how to realize the full potential of the material, that is, how to obtain the results that are potentially available from it, in areas that were not of direct interest to the inventors of the reference at the time. The Examiner's statement, that the Behr reference is relied upon for the step of applying a plasmid encoding an HIV protein to the skin of an animal, is ineffective because the Behr reference shows no such thing.

Claim Limitations Missing from the Behr reference

Among the differences between this reference and the presently claimed invention are that the reference does not disclose the transfection of antigen presenting cells, or the targeting of antigen presenting cells, a most significant subset of cells, and prominent by its omission, topical application of anything, or formulations that can be used for needleless, *in vivo* delivery of genes into any cells, much less antigen presenting cells, or any *in vivo* method of delivery except injection.

Similarly, the reference does not disclose that glucose and PEI derivatives could be used in the claimed method (Claim 24) or that the PEI derivatives can target the mannose receptor instead of the asialoglycoprotein receptors (Claim 25), or anything about mannosylated polyethylenimine (Claim 26) or the manipulation of electrostatically neutral complexes to target antigen presenting cells (Claim 28) or the specific ratio of PEI to DNA that is preferred for different derivatives (Claims 30 and 42), that the glucose solution should be preferred for targeting antigen presenting cells (Claim 31), or that the range of glucose concentration in a method targeting antigen presenting cells is higher than that disclosed for general use for transfecting neurons in the Behr reference (Claims 32 and 33),

or that a further step of receptor stimulation, tissue injury or cell injury might activate antigen presenting cells and therefore enhance a (disclosed in the Behr reference to be an undesired) immune response (Claim 35), or that proteins from human immunodeficiency viruses can be used in the claimed method to transfect antigen presenting cells (Claim 37), or that the claimed method would be successful using a nucleic acid sequence encoding an integration-defective or replication-defective human immunodeficiency virus (Claims 38 and 39), or that a plasmid DNA can be successfully used in the claimed method (Claim 40), or that Langerhans cells can be targeted using the claimed method and materials (Claim 41), or that use of a sugar-modified polyethylenimine would be desirable (Claim 43).

The Carson Reference (Evidence Appendix – 13)

The Carson reference is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin that transfects dendritic cells (col. 36-37, Examples 11-12). The definition of the complex is apparently plasmid DNA only, and is referred to repeatedly as "naked" e.g., Col. 30, line 41. These materials were formulated in saline solution (Col. 31, line 18). Both of the cited experiments rely on devices: intradermal injection of plasmid (Example X, column 35, line48) or a tyne device (Col. 37, line 16). Naked DNA formulated in a glucose solution was tested in the Behr reference Example 14, Col. 13, lines 9-10, injected and found not to work in that experiment. Similar results were obtained in an in vitro experiment using saline solution in the Behr reference at Example 13, Col. 12, lines 39-41). Also, the Carson reference reports both antibody responses (Col. 31, lines 54-56) and CTL responses (Example IX) which it attributes to the location of injection, intradermal rather than intramuscular. There is no discussion whatever about topical application, or how to target APCs according to the manner of the claimed invention. Further, it is noted that the later, Behr reference discussed above, tested the materials and methods of the Carson reference and found them ineffective.

The Holler Reference (Evidence Appendix – 14)

USPN 5,908,923 to Holler, et al. discloses and claims a sequence listing for a specific transdominant negative integrase gene which is said to be capable of making at least one cell resistant to a retroviral infection. This gene was used *in vitro* to transfect a lymphoblastoid cell line. The Examiner admits that this reference does not disclose any *in vivo* method.

The methods of transfection mentioned are calcium phosphate co-precipitation, cationic liposomes, electroporation, receptor mediated endocytosis, naked DNA,

transduction by viral vector, and particle-mediated gene transfer. The only method discussed, (which is also shown in the Examples) is calcium precipitation.

This disclosure simply amounts to a suggestion that the gene is useable. It says nothing about the claimed method. Indeed, this 1994 reference would appear to recommend that the gene can be successfully delivered by any and all methods. See Col. 7 lines 40-57. However, the present application discloses that an article published several years later compared transfection rates in antigen presenting cells and a cancer cell line (melanoma) that was known to be readily transfected by all the methods tested. (page 21, lines 2-4). This article reported only "low efficient" *in vitro* methods were known at the time, see page 6, lines 4-11 (cite to Arthur, J. F. et al., Cancer Gene Therapy 4:1 17-21, 1997 and Song, E. S., et al., PNAS USA 94:5, 1943-8, 1997[8]); and that neither they nor the known *in vivo* methods had been shown to effectively deliver genes to antigen presenting cells, much less delivery of genes through the skin into the Langerhans cells. See page 6, lines 16-19. Thus, this reference adds nothing to the cited combination.

The Examiner has stated that the applicants' comment that the Holler reference recommends the gene can be successfully delivered by any method, and that this is not persuasive because certain "low efficient" methods cited in the background section of the present application were said to be "successful." First, the application text discloses that these experiments were not successful. The application discloses that they had not been shown to effectively deliver genes to antigen presenting cells, much less delivery of genes through the skin. Further, the reference does not teach the claimed method, and it is the method, not the raw materials, that is lacking in the prior art. Christening the prior art "successful" doesn't change the fact that the new method is not disclosed in the prior art. The reference does not differentiate among types of cells, methods of gene delivery, or provide any basis to choose the present method from among many, successful or not. The claimed invention is not a given retrovirus, nor is it an adjuvant. It is a method of transfecting antigen presenting cells.

The Claimed Invention

A method of transfecting antigen-presenting cells, the steps comprising selecting a gene delivery complex that targets antigen presenting cells, comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter.

An advantage enjoyed by this invention is that the gene delivery complex need not be injected, but merely applied to the skin,[8] according to the claimed method. The inventors have found, and the text of the application contains, experiments that demonstrate that both the wholly novel complex (DNA plus mannosylated PEI) and several other arguably previously disclosed complexes (DNA plus modified PEI, PEI with sugars, PEI alone, and sugars alone) also work in an elegant method for stimulating the immune system that does not rely on injection, added irritants or toxins, use of cultured cells or expensive new equipment such as a gene gun.

Differences between the Claimed Invention and the Prior Art

Among the differences between the presently claimed invention and the primary reference (Behr) are that the reference does not disclose the transfection of, or targeting of, antigen presenting cells, a most significant subset of cells, and prominent by its omission, or formulations that can be used for needleless, *in vivo* delivery of genes into any cells, much less antigen presenting cells, or any *in vivo* method of delivery except injection. The reference does not teach or suggest the use of sugars to target the mannose receptor, the significance of having an electrostatically neutral complex in this context, the significance to the inventors' method of the ratio of nitrogen to phosphate, use of glucose solutions in the claimed range, any reason to prefer a glucose solution over a saline solution, or any further steps to enhance the response of the skin to the formulation. The other references do not supply any of the missing information.

The present application discloses how to modify the teachings of the Behr reference so that that the claimed method targets antigen presenting cells instead of neurons (at least at page 14, line 37 – page 15, line 15, and Example 6), in part by using a specific type of formulation based on multiple factors including the use of sugar-modified formulations and manipulation of a nitrogen/phosphate mol ratio to target a different receptor from that suggested by the Behr reference, and in part by refraining from using any injection method, that is, placing the formulation on the skin, and in part by using DNA encoding a specific class of materials undesired for the purposes of the Behr reference, immunogenic proteins. The transfected APC are capable of producing a CTL response (page 11, line 21), which is toxic for the purposes of the Behr reference (Col. 1, line 51), Additional data submitted by the inventors shows that the immune response induced in this manner does not include antibody (humoral) responses using either the (injected) *ex vivo* or (applied to the skin) *in vivo* procedures. Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus

[8] Evidence Appendix 10

Type 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells"[9] J Virol, Aug 2001, p. 7621-7628, at p 7626, lines 12-15, 1st full paragraph. See also Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/AIDS J Inv Dermatology, 2004,[10] p. 6, col. 1, first paragraph, last 4 lines, and second paragraph, lines 2-4.

C. Analysis

1. The Prima Facie Case – the References and their Combination

The present rejection does not establish a *prima facie* case of obviousness against the amended claims because the claimed method is not present in any of the references individually, or their combination. As discussed in more detail in the 35 USC § 102 rejection above, the Behr reference does not inherently disclose the claimed method, with or without the support of the Carson reference. The Behr reference must be modified in order to derive the claimed invention. The present application discloses how to modify the teachings of the Behr reference so that that the claimed method targets antigen presenting cells (a different class of cells from neurons) (at least at page 14, line 37 – page 15, line 15, and Example 6), which are capable of producing a CTL response (page 11, line 21), which is toxic for the purposes of the Behr reference (Col. 1, line 51), in part by using a specific type of formulation to target a different receptor from that suggested by the Behr reference, in party by using DNA encoding a material undesired in the Behr reference, namely an immunogenic protein, and in part by refraining from using any injection method, that is, by placing the formulation on the skin.

The question presented here, therefore, is whether the cited references contain teachings sufficient for one of ordinary skill in the art to conclude the proposed modifications would work, without rendering the Behr reference inoperative.

The Carson reference is said to teach a gene delivery complex applied to the skin that transfects dendritic cells. This is not strictly true, for the "complex" is just plasmid DNA, and both of the experiments relied upon by the Examiner use injection devices. Further, plasmid DNA alone, in both saline (Experiment 13) and glucose solution (Experiment 14) was used in the Behr reference and found to be ineffective. And the Applicants have submitted evidence that, by the time the present invention was made, it had become known that different types of cells had different sensitivities to transfection, so that the older reference would not be considered by one of ordinary skill in the art to assure success with another. See Arthur, et al "A Comparison of gene transfer methods in human

[9] Evidence Appendix 6
[10] Evidence Appendix 4

dendritic cells" Cancer Gene Therapy, v. 4, No. 1, 1997 pp 17-25[11], which reports that the then-known *in vitro* methods of gene transfer suffered from low efficiency. The application also discloses at page 6, line 14-19 that, as of 1998, "known *in vivo* methods include ... intradermal subcutaneous and intramuscular injection of DNA. None of these methods have been shown to effectively deliver genes into antigen presenting cells, such as dendritic cells, much less delivery of genes through the skin into the Langerhans cells." See also the Pollard reference discussed at page 15, lines 3-6. [12] One of the conclusions drawn by the authors of that 1998 article was that barriers to gene transfer vary with cell type (Abstract, and p. 7510, col. 2, last full para, lines 1-8 UP). This disclosure is especially credible in light of the Examiner's vigorous insistence, in another context, that the art was at the time unpredictable. Thus the Carson reference is only useful as a disclosure of a raw material that has not yet been made to work.

The Examiner does not assert that the Holler reference teaches anything about the claimed method, only that it teaches the existence of a plasmid encoding a replication-defective, integrase defective HIV. Assuming the raw material is as described, there is still no description of the claimed method.

Neither the secondary nor tertiary reference, nor their combination, present any modification to the base reference, other than to suggest raw materials. They have nothing to add to the claimed method. The *prima facie* case for obviousness has not been made, and this rejection must be withdrawn.

2. Secondary Considerations – Objective Evidence of Non-Obviousness

Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present.

A vaccine according to the currently claimed invention is in human clinical trials in two countries. It is noted that clinical trial results are expressly NOT required according to the MPEP, however, the MPEP also acknowledges that "Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. MPEP 2107.02. It is respectfully submitted that acceptance for human clinical trial is not only evidence of the asserted therapeutic utility, but also some objective evidence of nonobviousness.

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[11] Evidence Appendix 10
[12] Evidence Appendix 11

A statement listing the trials can be found at [13]
http://www.geneticimmunity.com/pages/906725/index.htm
A Declaration to this effect was offered by the Applicants, but ignored.

Note: Examiner's Contention – Antigen Presenting Cells

Claim 23 has been amended so that the complex must target antigen presenting cells. This limitation must now be given patentable weight. The Examiner states without offering any rationale that "transfecting antigen presenting cells" "may not occur." The applicants have pointed out that the evidence that "transfecting antigen presenting cells" has occurred is in the text of this case and is copious. With the claims amended so that the limitation is in the body of Claim 23, this limitation must be considered. MPEP 707.07(l).

Examples in the application present evidence that APCs were indeed transfected. They were transfected *in vitro* using the best available prior art material for antigen presenting cells, lipofectamine (Example 1, plasmid DNA encoding HIV-1/LWint-, an integration and replication defective HIV described in one of the inventors' other applications, showing production of various proteins; Example 3 demonstrates that these cells developed the desired CTL response *in vitro*). They were transfected *in vitro* using PEI, showing that PEI worked better than lipofectamine, in Example 5. The PEI-transfected cells were shown to produce an *in vivo* CTL immune response in Example 4.

DC were transfected with a plasmid encoding green fluorescent protein and a variety of other adjuncts *in vitro*, including various PEI derivatives (Example 6).

Antigen presenting cells were transfected according to the method in Example 8, using a plasmid encoding green fluorescen protein where the claimed complexes were applied to the skin of mice (page 22, line 37) and then skin samples were tested for transduction of Langerhans cells, and it was found that a sugar modified gene delivery system is preferred to transduce antigen presenting cells. (page 23, lines 19-20). Example 9 shows that the claimed complexes also migrated to the lymph nodes and expressed protein (page 24, lines 6-7).

Note: Motivation

The Examiner's citation of the Holler reference for a desire to use attenuated HIV as a raw material for vaccines does not supply the teaching needed to derive the claimed method. Further, the cells that were transfected were cancer (lymphoblastoid) cells in vitro, by electroporation. It says nothing about transfection of antigen presenting cells *in vivo*, by applying a formulation on the skin. Given the disclosure in the present application, and in the references cited therein, that such methods of transfection were not effective, and that

[13] Evidence Appendix 8A

barriers to gene transfer vary with cell type, this reference cannot be said to supply either the kind of specific teaching or the expectation of success required to support an obviousness rejection.

D. Conclusion

In view of the above analysis and the evidence, it is respectfully submitted that the present rejection is inapplicable to the amended claims because neither the individual references nor their combination yield the claimed invention, and the case is well-supported by experimental results and secondary considerations, the impact of which have been acknowledged by peer-reviewed publications and the United States Food and Drug Administration.

Conclusion

For all the above reasons and amendments, it is believed that all the Examiner's legitimate concerns have been fairly met. Favorable consideration is solicited.

Respectfully Submitted,

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